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FEBRUARY 1952

VOLUME 65 NUMBER 2

Published Monthly by

AMERICAN MEDICAL ASSOCIATION

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References:

1. Rothman, J. and Shapiro, A. L.: Med. Clin. N. Amer. 33:274-5, Jan., 1949.
2. Stieglitz, E. J.: Geriatric Medicine, p. 848, 1943.

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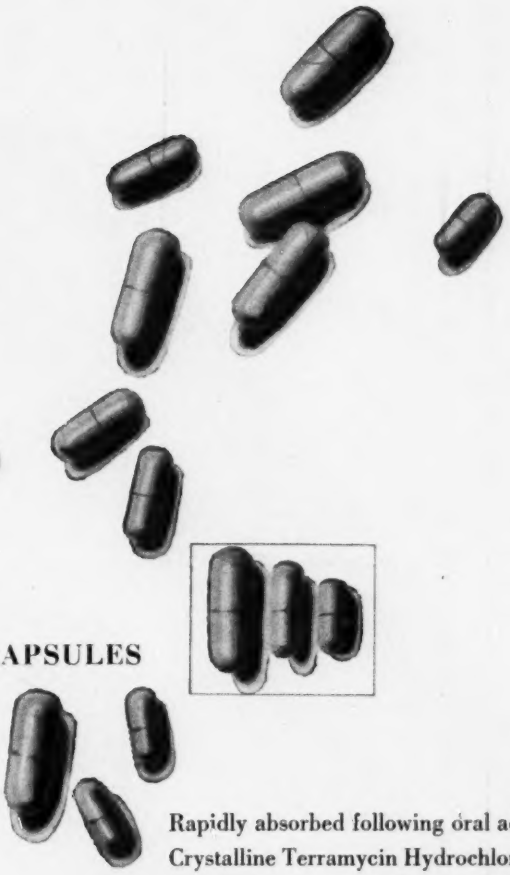

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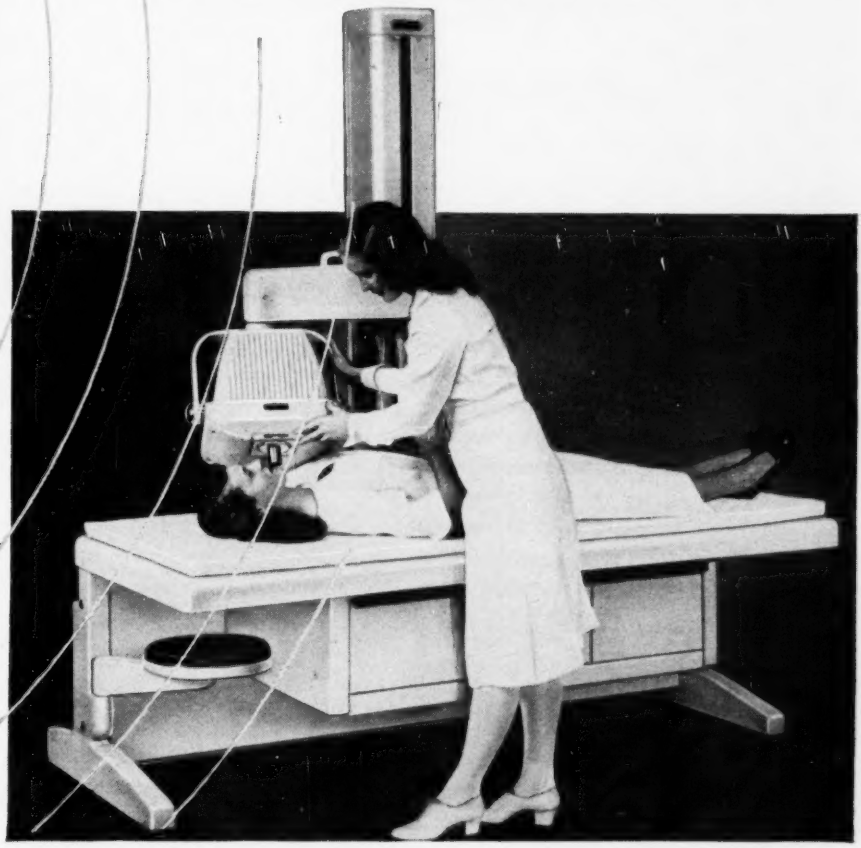

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1. Combes, F. C.: Coal Tar in Medicine. Industrial Medicine **13**:550-552 (July) 1944.
2. Combes, F. C.: Coal Tar in Dermatology. Arch. Dermat. and Syph. **56**:583-588 (Nov.) 1947.
3. Ellis, C. C.: Wooldridge, W. E., and Weiss, R. S.: J. Invest. Dermat. **10**:6 (June) 1948.

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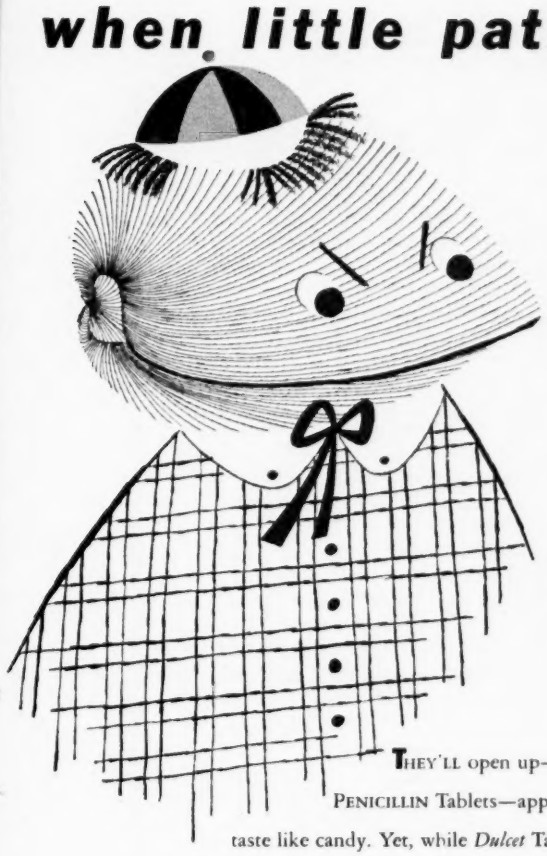

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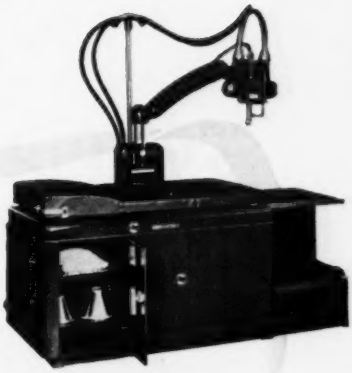

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Communications regarding subscriptions, reprints, etc., should be addressed, A. M. A. ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY, American Medical Association, 535 North Dearborn Street, Chicago 10.

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Archives of Dermatology and Syphilology

VOLUME 65 FEBRUARY 1952 NUMBER 2

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ANGIOSARCOMA IN POSTMASTECTOMY LYMPHEDEMA (STEWART-TREVES SYNDROME)

MAX JESSNER, M.D.
FREDERICK G. ZAK, M.D.
AND
CHARLES R. REIN, M.D.
NEW YORK

THE SYNDROME characterized by the appearance of cutaneous lymphangiosarcoma in the ipsilateral arm, years after radical mastectomy for carcinoma, has been described by Stewart and Treves.[1] We had occasion to see a patient with this until recently unknown disorder.

REPORT OF A CASE

A. N., a 54-year-old, white, single woman, a patient of Dr. H. Wadro, had a radical mastectomy in 1942 for carcinoma of the left breast, with axillary node involvement, followed by extensive x-ray treatment and, several months later, by radium therapy to the axilla.

Edema of the left arm developed shortly after the operation but regressed to about 50% in recent years. It was most conspicuous above the left elbow, where the arm measured 11½ in. (29 cm.) as compared with 8 in. (20.3 cm.) above the right elbow.

In April, 1949, the patient noticed bluish, firm, raised nodules on the inner aspect of the left arm outside the x-ray-treated area. These grew slowly in number and size. Some were removed by Dr. A. Kaye. One of these lesions was diagnosed elsewhere histologically as a "benign blood tumor" in May, 1949. Other nodules were cauterized, but new ones continued to appear. On Sept. 28, 1949, she was first seen by one of us (C. R. R.). At that time she presented typical x-ray sequelae on the left anterior chest wall, extending into the axilla up to the shoulder and down to the junction of the first and second quarter of the flexor surface of the left arm. A skin defect was still present in the apex of the axilla.

On the inner aspect of the left arm, distal to the area of the skin treated with x-rays, there were firm, bluish, cutaneous and subcutaneous nodules. Similar smaller lesions could be seen above the medial epicondyle.

When seen a week later, new nodules of the same aspect had made their appearance. This process continued during the next few weeks. On Nov. 19, 1949, one of the larger lesions was excised by Dr. A. Kaye. The tissue sections were studied at the New York Skin and Cancer Hospital, where the diagnosis of lymphangiosarcoma of the type described by Stewart and Treves was made by one of us (F. G. Z.).

A chest radiogram taken at that time was reported as normal. From Dec. 15 to Dec. 29, 1949, the patient was treated with 3,500 r to a tumor-bearing area, 4 cm. in diameter, by

---

Presented at the Seventy-first Annual Meeting of the American Dermatological Association, May 26, 1951, Hot Springs, Va.

From the Department of Dermatology and Syphilology of the Post-Graduate Medical School of New York University-Bellevue Medical Center (Dr. Marion B. Sulzberger, Chairman), and New York Skin and Cancer Hospital.

1. Stewart, F. W., and Treves, N.: Lymphangiosarcoma in Postmastectomy Lymphedema: A Report of 6 Cases in Elephantiasis Chirurgica, Cancer **1**:64-81, 1948.

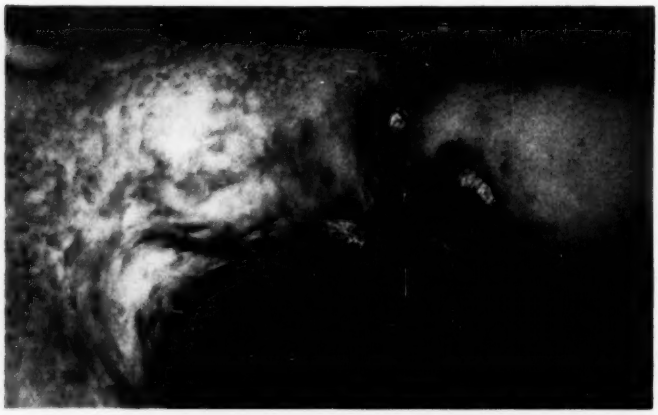


Fig. 1.—Biopsy wound is healing, Feb. 13, 1950, but new tumors have formed in the vicinity.

Fig. 2.—Amputation has failed to halt the proximal spread of the disease, May 2, 1950; sutures indicate the site of young lesion referred to in text (and Fig. 7).

Dr. M. Friedman. This was done to determine the radiosensitivity of the lesion. There was but negligible response to this therapy. This was borne out by histologic examination, in view of which finding it was decided to amputate the arm. In the meantime the tumors had grown considerably (Fig. 1). The amputation was performed by Dr. A. Kaye on March 6. Unfortunately, the resected limb was not examined. The patient returned to her home in another state and was again seen on April 20, at which time she was presented at a meeting of the Bronx Dermatological Society. It was then apparent (Fig. 2) that the amputation had failed to halt the spread of the disease, yet there was no evidence of pulmonary metastasis upon roentgenologic reexamination.

The patient returned to her home town, where she was hospitalized on June 5 because of increasing dyspnea.[2] About six weeks prior to this admission, masses had appeared in the right (contralateral) axilla and clavicular fossa, soon followed by dyspnea. The physical examination at the time of admission disclosed some weight loss and impaired resonance over the whole left

Fig. 3.—Very low-power photomicrographs showing large ill-defined ovoid cellular tumor in corium; hematoxylin and eosin.

chest. Chest radiographs revealed osteoporotic lesions involving the second to the eighth ribs on the left, with partial destruction of the scapula and the clavicle on this side. The left lung field was obliterated, and nodular areas were seen throughout the right thorax. Secondary anemia (hemoglobin, 9 gm.; hematocrit, 29%) was present. The patient's course was progressively downhill with increasing pain until she died on July 12, 1950.

Autopsy disclosed sloughing of the recent amputation wound, numerous tumor nodules proximal to the amputation site and on the left chest wall, where they were found to penetrate to the costal fascia, while those on the right chest wall were subcutaneous. The lower portion of the old mastectomy incision was eroded. The left lung was completely collapsed and appeared as a small mass compressed by dense, rubbery, grey, seemingly neoplastic tissue which obliterated the pleural space and occupied the anterior mediastinum. The right anterior cervical and infra-

2. Dr. D. Yuter, the patient's private physician, and Dr. R. E. Palmer, both of Alexandria, Va., supplied the follow-up data. The latter performed the autopsy.

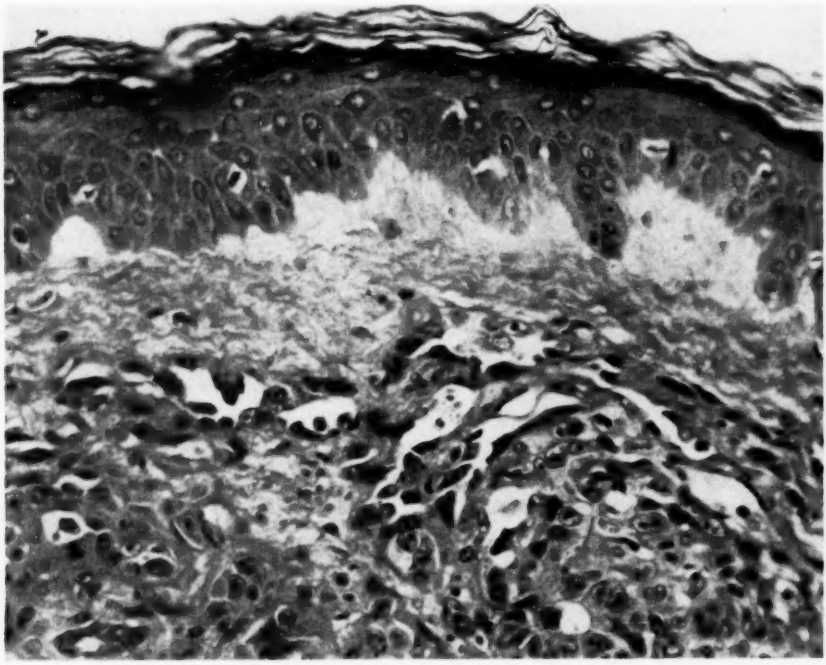


Fig. 4.—Higher power photomicrograph showing well-demonstrated vesicular nuclei and abortive formation of channels; hematoxylin and eosin.

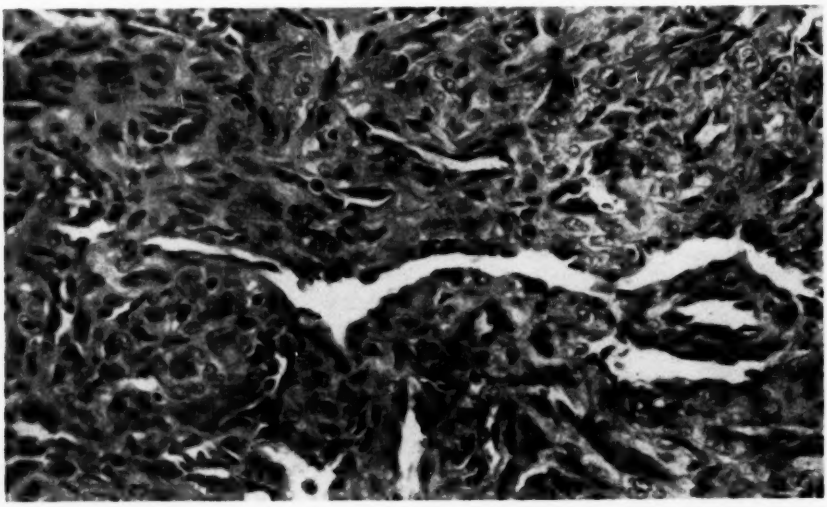


Fig. 5.—Many empty branching channels of more mature appearance than in Figure 4; hematoxylin and eosin.

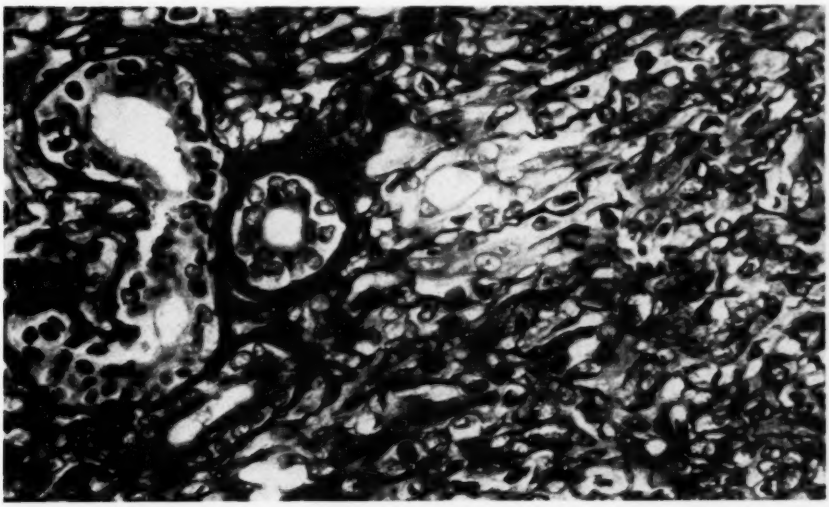


Fig. 6.—Fine reticulin network surrounding tumor cells singly or in small groups; compare with heavy basement membrane of sweat gland; Wilder's silver impregnation.

Fig. 7.—Section from lesion presumably five days old; spindle-cell tumor between collagen bundles of corium. Angiogenesis is negligible, thus the picture is not diagnostic; hematoxylin and eosin.

clavicular nodes were involved by tumor. Microscopic studies showed tumorous involvement of the fibrotic left lung, one of the above-mentioned lymph nodes, and the subcutaneous tissue of the right thorax.

The histologic findings of the tumor tissues removed during life were as follows. The advanced lesion appeared as a cellular growth (Fig. 3) which displayed bullous edema of the upper corium, with acanthosis and central crusting of the overlying epidermis. This edema faded out on each side, the corresponding epidermis likewise becoming normal. The underlying tumor extended almost to the level of the rete pegs in the nonedematous parts (Fig. 4) and appeared as a cellular growth with ovoid or fusiform, pale nuclei and large vesicular nuclei with prominent nucleoli frequently close to each other, resembling certain poorly differentiated carcinomas (e. g., from the pharynx or thymus) as well as dark-staining, slender nuclei. Angiogenesis was fairly prominent (Figs. 4 and 5) and ranged from abortive attempts at formation of capillary type vessels to lacunar structures, mostly empty, but occasionally containing amorphous precipitated matter. It is possible that the occurrence of red cells in some of these spaces was due to trauma incidental to biopsy. Other similar spaces undoubtedly contained blood before removal, thus accounting for the grossly livid appearance of the lesions and justifying the term hemolymphangiosarcoma, or "angiosarcoma," to denote the presence of blood capillaries as well as lymphatics. Some of the vessels formed by the tumor were lined with large cells bulging into the lumen, showing mitotic figures on occasion. In the deeper portions mitoses were quite numerous. The subcutaneous fat was invaded, and the skin appendages had largely disappeared except for the arrectores pilorum.

The destruction of the preexisting collagen was demonstrated by a trichrome stain (Mallory-Heidenhain) which also showed a fine, newly laid-down collagen network in many areas with fibrils surrounding individual cells. Wilder's silver impregnation revealed that the majority of the tumor cells, either singly or in groups, were enwrapped by reticulin fibrils (Fig. 6). Wherever there was destruction of collagen, the elastic tissue likewise was destroyed.

A small, newly developed nodule (Fig. 7) showed irregular accumulations of cells with spindle-shaped or ovoid nuclei, poor in chromatin, between the collagen bundles of the corium. There was little tendency to angiogenesis and scant resemblance to the fully developed lesion. Mitotic figures were observed as well as edema of the corium.

COMMENT

The following salient clinical and pathologic features are brought out in the reports by Stewart and Treves [1] and Ferraro.[3]

All reported cases [4] occurred in women 46 to 68 years old. Various degrees of postoperative edema of the arm are an early and eventually a permanent sign. The time interval between the operation and the appearance of lymphangiosarcoma varied in these seven cases from 6 to 24 years. As 70% of patients undergoing radical mastectomy demonstrate swelling of the arm,[1] knowledge of the disorder assumes practical importance. Daland [5] recently summarized the subject of postmastectomy elephantiasis and stressed certain points to be observed in order to avoid this complication. Since these tumors are not radiosensitive, early and radical amputation may prove a lifesaving procedure. The pathologist, likewise, should become familiar with this syndrome and consider it whenever a Kaposi's-sarcoma-like picture is encountered in lymphedema, clinically and microscopically, following mastectomy.

3. Ferraro, L. R.: Lymphangiosarcoma in Postmastectomy Lymphedema: A Case Report, Cancer **3**:511-514, 1950.

4. Dr. Arthur Purdy Stout knows of three unreported cases of this condition (Stout, A. P.: Personal communication to the authors). Dr. W. A. Fraser has another case in his files (Fraser, W. A.: Personal communication to the authors).

5. Daland, E. M.: Prevention of Swollen Arm After Mastectomy, New England J. Med. **242**:497-502, 1950.

Not having been able to perform microscopic examinations of the amputated arm, our findings are not as complete as the excellent descriptions in the article by Stewart and Treves which are based on examination of amputated arms in addition to skin biopsies. Thus, formation of lymph follicles and perivascular arrangement of tumor around deep veins, also seen by Ferraro,[3] was not observed by us. In our case there was a tendency of tumor cells to deposit reticulin. This feature was not mentioned in the original article. Since many of the lesions appear dark red clinically, we consider that they must consist of a mixture of lymphatics and blood vessels rather than being purely lymphangioblastic, an observation corroborated by microscopic examination, even with due allowance for hemorrhage caused by biopsy trauma.

We concur with the first observers that radiation treatment is not effective for this condition and that early radical, i. e., interscapulothoracic, amputation is indicated as soon as a definite diagnosis is made.

The absence of tumors of this nature in elephantiasis not related to cancerous disease, e. g., filariasis, has led Stewart and Treves to postulate the presence of a carcinogen which, under favorable conditions like chronic lymphedema, will produce an angioblastic tumor. It is up to experimental workers to study this thesis. In this connection, it should be stressed that the lesions of Kaposi's sarcoma may be preceded by chronic edema.

Another possible explanation might be found in the startling observation of Toolan and Kidd,[6] who found that mammary carcinoma cells which had sojourned in immune mice produced sarcoma-like pictures, including the property of reticulin formation. The possible connection between this observation and the Stewart-Treves syndrome is obvious but remains to be proved.

SUMMARY

A case of fatal angioblastic sarcoma arising in a chronically edematous arm seven years after radical mastectomy and radiation therapy for carcinoma is described (Stewart-Treves syndrome). This lesion must be differentiated clinically from metastatic carcinoma and Kaposi's sarcoma and histologically from the latter. The treatment consists in early interscapulothoracic amputation to prevent pulmonary metastases. No time should be wasted with irradiation, as the lesions respond poorly, at best.

ADDENDUM

A case of this condition was described in the "Color Atlas of Pathology," prepared under the auspices of the United States Naval Medical School of the National Naval Medical Center, Philadelphia, (J. B. Lippincott Company, 1950, p. 243), and labeled as Kaposi's sarcoma.

870 Fifth Ave.

25 E. 94th St.

580 Fifth Ave.

6. Toolan, H. W., and Kidd, J. G.: Sarcomatoid Growths Resulting from Mammary Carcinoma Cells That Had Sojourned in Immune Mice, Federation Proc. **9**:346, 1950.

DERMATOLOGICAL WRITINGS OF SIR JONATHAN HUTCHINSON

JACK E. McCLEARY, M.D.
AND
EUGENE M. FARBER, M.D.
SAN FRANCISCO

SIR JONATHAN Hutchinson is regarded as our last great multispecialist of medicine. He was a combination of teacher, naturalist, philosopher, and "a student and seeker after truth to the end of his days."[1] In the voluminous literature that has been written concerning him and his writings,[2] the best short description is that in an excerpt from an address by Sir William Osler[3]:

> He is the only great generalized specialist which the profession has produced, and his works are a storehouse upon which the surgeon, the physician, the neurologist, the dermatologist and other specialists freely draw. When anything turns up which is anomalous or peculiar and cyclopaedias are dumb, I tell my students to turn to the volumes of Mr. Hutchinson's Archives of Surgery, as, if it is not mentioned in them, it surely is something very much out of the common.

His contributions to the various fields of medicine are numerous and well documented by the eponyms found throughout the medical literature. Hutchinson's triad, syndrome, facies, whitlow, pupil, disease, mask, varicella, etc., are but a few and represent him well when he is grouped with such contemporaries as Stokes, Addison, Hodgkin, Paget, Charcot, Claude Bernard, and Ehrlich.

Along with his reputation as a very prolific author he was known as a collector and teacher of many subjects. In his Educational Museum at Haselmere, where he gave weekly widely variegated lectures, he had gathered an extensive collection of specimens of natural history, books, maps, charts, historical portraits, etc. Bird skeletons, insects, rocks and fossils, and a synopsis of the history of the centuries, beginning with the Egyptians and ending in the Victorian era, which extended for 600 ft. along one wall, were but a few of its many attractions. Study became such a part of him that in his last days, when it became necessary for him to remain indoors, he studied the tumors on wood which was brought to his fireplace.

From the Division of Dermatology, Department of Medicine, Stanford University School of Medicine.

1. Nettleship, E.: Sir Jonathan Hutchinson, Ophthalmoscope **11**:504, 1913.

2. (*a*) Selections from the Writings of Sir Jonathan Hutchinson, 1828-1913, M. Classics **5**:109-245, 1940. This compilation contains a bibliography and a list of biographic references. (*b*) Bruce, G. M.: Last of the Multispecialists, New York Acad. Med. **13**:539-545, 1937. (*c*) Osler, W.: Sir Jonathan Hutchinson, Philadelphia M. J. **4**:453-455, 1899. (*d*) Klauder, J. V.: Sir Jonathan Hutchinson, Med. Life **41**:313-326, 1934. (*e*) Pusey, W. A.: The History of Dermatology, Springfield, Ill., Charles C Thomas, 1933, pp. 128-131.

3. Osler, W.: Importance of Post-Graduate Study, Lancet, 1900, quoted in Osler, W.: The Sir Jonathan Hutchinson Iconography, Bull. Johns Hopkins Hosp. **26**:82-83, 1915.

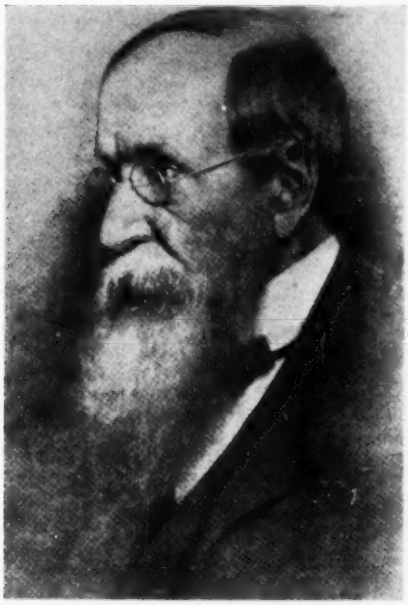


Fig. 1.—Sir Jonathan Hutchinson, 1828-1913.

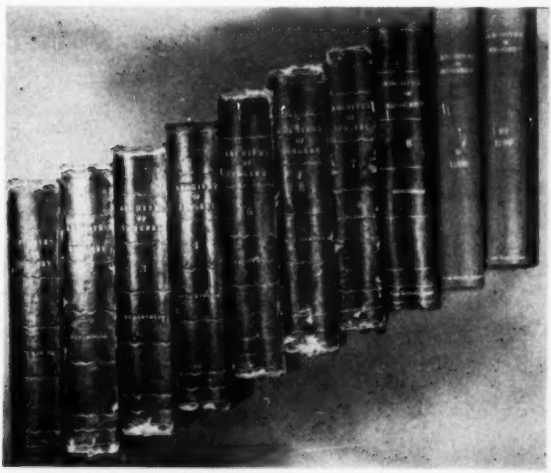


Fig. 2.—*Archives of Surgery*, published from 1889 to 1899, in which every report was written by Sir Jonathan Hutchinson.

Like his classmate, Lister, who preceded him by one year in birth and death, Sir Jonathan came from an old Quaker family. His father was a prosperous "middleman in the flax trade," and Jonathan was the second of eight sons. He was born in Selby, Yorkshire, in 1828, and was educated by a Quaker governess. In 1845 at the age of 17 he was apprenticed to a Quaker surgeon, Mr. Caleb Williams, and a year later entered the small school of medicine at York. When he was 21, he went to London to St. Bartholomew's Hospital for clinical instruction. At 22 he became a member of the Royal College of Surgeons of England. In 1854, at the age of 26, his first appointment was to the Blackfriars Hospital for Diseases of the Skin.

The beliefs of his Quaker background, the times of Victoria, and the progress of the social and medical fields about him have been used to explain the various facets of this man. He is commended for the founding of the second New Sydenham Society which produced a large number of popular-priced atlases (to which he contributed "Atlas of Skin Diseases"). His weekly clinical demonstrations in his later years have been described as a "mecca of London medicine." It has been pointed out that his attempts at postgraduate instruction were before his times, and his private clinical museum was given little approval by the London medical profession of that time.

Others have held his industry as overzealous, his utter beliefs as dogmatism. Supposedly, patients invented relatives with certain afflictions in order to satisfy his persistent questions of family background. Occasionally the patient's denial of preceding disease fell on deaf ears when he was convinced of the pathological conditions. He is described as a free lance, giving any dermatosis that was unknown to him a name, sometimes using that of the patient, and adding confusion to the terminology. To this very evil he expressed himself [4]:

> We must remember that, "the name of a thing is that which it is known by," and that most names are mere matters of convenience to facilitate the communication of knowledge. It follows, then, that names ought to be used as much as possible in the sense which custom has assigned them, and that attempts to go back from general usage to strict etymology, or to the original meaning of Greek or Roman authors, are in the present day little less than impediments to progress. It follows, also, that names should never be used to substitute knowledge or to conceal ignorance. We have to study the science of causes, not the art of giving names.
>
> If it be true that:—
>
> "Those earthly godfathers of Heaven's lights
> Who gave a name to every fixed star,
> Had no more pleasures of their shining lights
> Than those who walk and wot not what they are."
>
> it is, certainly, as true that those who have been most liberal in dermatological name-giving, have sometimes rather hindered than advanced the real knowledge of the maladies which they have tried to dignify.

4. Hutchinson, J.: Hints as to Study of Skin Diseases, Lect. & Rep. London Hosp. **1**:162-176, 1864. Dr. Arthur L. Bloomfield called to our attention that the lines from Shakespeare in this passage were misquoted and should read as follows:

> "These earthly godfathers of heaven's lights
> That give a name to every fixed star,
> Have no more profit of their shining nights
> Than those that walk and wot not what they are."
> (Love's Labour Lost, Act. 1, Scene i, Line 86)

In the study of causes and their results, we must always remember that, very frequently, two or more are at work at the same time, and that even when the causes are simple and definite, still the individuals upon whom they are brought to bear, are in but few instances exactly alike in susceptibility. Hence the great difference as to appearance and results which a cause so single and definite as that of scabies may produce in different persons.

It seems to be a necessity, if skin diseases are ever to become part of an ordinary medical education, that we should get rid of a great number of the names and adjectives which now encumber the subject. Not even a professed dermatologist can keep in memory the meanings of many of the terms now met with in our books.

It is difficult to explain some of his honest persistence. To the study of leprosy he probably devoted more time than to any other single subject. Concerning the cause of leprosy, he stated [5]

that the poison which produces the disease gains access to the body in the form of food; that the evidence as regards this disease points to fish as being probably the vehicle by which the poison of leprosy gains access to the human body.

It is evident that the disease, if contagious at all, is so in the feeblest possible manner. Its main cause of spreading is certainly not contagion. Nor does it spread solely or chiefly by inheritance, for an Englishman going to live in a leprosy district may acquire it in a year or two. It cannot possibly be due to any telluric emanations of the nature of malaria or otherwise, for it occurs in much different places, and it affects comparatively few in each place. It has clearly nothing to do with temperature or climate. Nor is it a result of poverty or of neglect of the ordinary rules of life, for it attacks in both Indies persons who have enjoyed every comfort and have never deviated in any way from the strictest purity of outward life (young children for instance). It is clear then, I submit that the poison must be taken inadvertently in connexion with some kind or kinds of food. No other hypothesis can be suggested which in any degree adequately meets the facts, and this one does so. What articles of food are we to suspect?

In pursuit of facts to support his beliefs he visited South Africa and India at an age when other men would have been content to enjoy a well-earned leisure.

In some other arguments he fared better. In 1874 he took part in a discussion which brought forth his noted contemporaries, including Paget and Broadbent, regarding a local versus a constitutional origin of cancer. He stated: [6]

I headed a short article that I wrote, ten years ago, in the "London Hospital Reports" "The successful cultivation of cancer," and in it I ventured to give precise directions to those who wished to let their cases pass into cancer how they should do it. My suggestions were that patients with hard-edged ulcers on the tongue should be told to touch them once a week with caustic and come again in three months; the man with a wart on his lip allowed to go on smoking a short pipe and picking the top occasionally, and the subject of a little glossy-edged sore on the eyelids confidently assured that it was of no consequence and might be left to itself and cold cream. I felt great confidence—trusting to the theory of local origin—in recommending such measures as are tolerably certain to be the worst forms of cancer. My reason for adopting that title, and for using the style I did, was that I desired to direct the attention of students, and of the profession, to the practical importance of acknowledging the local origin of a great number of forms of cancer, and to the paramount necessity for very early treatment, if we wish to secure our patients against becoming constitutionally affected.

His place in dermatology in the latter half of the last century is shadowed by Erasmus Wilson and Tilbury Fox, but as a representative of clinical dermatology he had few equals. It is said that, taking the whole field of medicine for his domain,

5. Hutchinson, J.: The Leprosy Problem, Arch. Surg. **1**:i-xxii, Appendix, 1890.

6. Hutchinson, J.: Remarks on Discussion of Cancer, Tr. Path. Soc. **25**:310-314, 1874.

he could not be a finished dermatologist, but in his lifetime he contributed or was author of nearly 600 published articles or case reports of skin afflictions.[2a] His "firsts" by the law of averages should be numerous. He contributed original descriptions or broadened the knowledge of many diseases, among them being the following:

Cheiropompholyx, described by Fox as dyshidrosis, and incompletely described by Bazin.

Mortimer's malady, a form of sarcoid.

Hilliard's lupus, resembling lupus verrucosus clinically.

Recurrent summer eruption of Hutchinson, similarly described by Bazin as hydroavacciniforme.

Solid edema of the face following attacks of lymphangitis, a form of elephantiasis.

Melanotic whitlow of Hutchinson, malignant melanoma arising in the nail bed.

Recurrent fibroid of the skin, a rare form of spindle-cell sarcoma.

Varicella gangrenosa, known also as dermatitis gangrenosa infantum.

Severe bullous eruptions produced by potassium iodide.

Penman's disease, severe acne which involutes to form scars.

Atrophic balanitis.

Nevus lupus, a rare condition of acquired cutaneous angioma, more generally known as angioma serpiginosum.

Lupus lymphaticus, described by Fox as lymphangiectodes is known now as lymphangioma circumscriptum.

Hutchinson described two cases:[7]

"In one case it began on the chin, by what looked like a little wart, at about the age of nine; and in the other on the shoulder, at the age of four, apparently the result of friction from the boy's braces. In each instance the morbid condition had spread near to the part first affected, but had not developed itself on any more distant region of the body. It consisted of groups of coherent vesicles, upon and amongst which were little tufts of dilated capillaries. There was some general thickening of the skin at the base of the vesicles; the latter, which were firm and very persistent, yielded a fluid which was not distinguishable from lymph. There was no outgrowth of papillae whatever. The character of the eruption was remarkably the same in all parts, varying chiefly in the presence or absence of the little capillary tufts. There was no discharge of any kind from the eruption, but the patches were liable to attacks of erysipelatous inflammation. The treatment adopted consisted in destroying the patches by caustics and the actual cautery."

Herpes zoster following arsenic administration.[8]

"In arsenical herpes zoster we have a definite form of peripheral neuritis, but it is far from being the only disturbance of nutrition which we witness in connection with the use of this powerful drug."

"I prescribed arsenic, in very full doses, for Mrs. E——, in order to cure psoriasis of the nails. It was effectual; and she took it regularly for several months. In March, 1888, she reported to me that about the previous Christmas she had suffered a most severe attack of shingles on the right side of her chest. Her surgeon, in Yorkshire, where she was, had told her that he had never seen a case with so much inflammation. Fortunately for me he had not suggested to her any suspicion as to its having been caused by the medicine."

Malignant freckles of Hutchinson, described later as melanose circumscripta precancereuse by Dubreuilh, consisting of pigmented spots which are potentially malignant.[9]

7. Hutchinson, J.: Lupus Lymphaticus, Arch. Surg. **1**: Plate XV, 1890.

8. Hutchinson, J.: Arsenic as a Cause of Herpes Zoster and Dull Eyes, Arch. Surg. **1**:75-76, 1889.

9. Hutchinson, J.: Lentigo-Melanisos, Arch. Surg. **5**:253-256, 1894.

"Apart from the importance of their clinical recognition, much interest appears to me to attach to this group of cases as illustrating the laws under which physiological processes slide into malignancy. We have first freckles such as are seen on the eyelids of many elderly persons, these become very black and enlarge. Next the freckles coalesce, and we have a patch which is infective at its edges, and which may extend to the adjacent mucous membrane and even to the cornea of the eye. Still there is nothing to be called new growth, the process being simply one of pigmentary staining without appreciable thickening. Lastly, however, another stage is assumed, and a growth takes place which is for the most part unpigmented, and which in its tendency to break down and ulcerate reveals its malignant nature. In some cases this final growth is of epitheliomatous structure, and in other sarcomatous. This form of disease is not limited to the eyelids, although the most typical examples are seen on them. I have already described examples of it on the lips and on the prepuce."

In his clinical lectures his descriptions are vivid and developed to furnish the point of comment.[10]

Gentlemen—Margaret M., the girl now before us, is suffering from an inflammation of the skin, which has produced, on various parts, numerous, large, watery blebs. These blebs are scattered over her arms, shoulders, chest, abdomen and thighs, in some parts they are quite separate from each other, and abruptly round; in others a group has become confluent. Thus, on the inner aspects of her thighs are confluent clusters as large as the out-spread hand. You see these blebs in very different stages, some not larger than peas, beautifully transparent and pearly, others as large as half a marble or even ¾ of an inch in diameter and still transparent, or only a little yellow, whilst many contain pus and are quite opaque. Many others have collapsed, leaving only superficial sores, covered with loose white layers of epidermis. The poor girl looks, indeed, as if she had been splashed over every day, for a week, with blistering fluid. We much note, however, that there is nothing suggestive of accident about the arrangement of the patches, they are almost exactly symmetrical on the two sides. From this we infer with confidence, that they are caused not by an external irritation, but by some internal irritant circulating with the blood, and by it distributed in exactly equal shares to each half of the body. It is, therefore, not a skin disease in the restricted sense of the term, but merely a symptom presented by the skin indicative of humoral disorder.

With his clinical observations he adapted available instruments to further investigations. The ophthalmoscope owes much to his constant stress of its importance (along with Hughlings Jackson) and likewise the microscope in dermatology.[11]

The case was important as an illustration of the great value of the microscope in the diagnosis of affections of the scalp. Without its aid, it would have been impossible for the most experienced dermatologist to have conjectured the true nature of the disease.

It was with such microscopic evidence that he disproved a contemporary's (Mr Wilson's) fatty degeneration theory of ringworm.

To fully appreciate Hutchinson one must follow the advice of Osler given in our first paragraph, for in the 11 books which comprise the *Archives of Surgery* we see a collection of notes and dissertations contributed wholly by Hutchinson, which causes the most skeptic to marvel. Here we see a museum placed before us, each plate showing a clinical masterpiece.

Hutchinson's activity in dermatology was rewarded in 1896 when he was elected president of the International Dermatological Congress. And for his activity the

10. Hutchinson, J.: On Cases of Relapsing Pemphigus, Clin. Lect. & Rep. London Hosp. **1**:162-176, 1864.

11. Hutchinson, J.: Hair and Crusts from a Case of Ringworm, Showing Peculiarities in the Growth of Characteristic Fungus, Tr. Path. Soc. **7**:395, 1856.

field of dermatology is greatly indebted. In his epitaph in 1913 it was held that "Modern research exacts such a development of specialism that we can never expect to see combined in one person the all-round excellencies of Jonathan Hutchinson."[12] Nor in dermatology can we expect such industry and endeavor to reach us often through our times.

His remarks are long-lived[13]:

> Dermatology is no longer to be regarded with senseless prejudice, as a mere matter of giving arsenic and prescribing ointments and lotions, nor, as some, only a stage more enlightened, think, an arena for endless debate as to the arbitrary application of pedantic names of older or newer coinage. We have got beyond the old classification, and we are ceasing to be merely empirical therapeutists. We claim for dermatology a foremost place as a branch of scientific medicine, and without hesitation I assert of it that beyond all others it offers attractions to the student of laws of disease in general, and to the seeker after the causes which disturb health and local nutrition.

Stanford University Hospitals (15).

536 Mason St. (2).

12. Obituary, Brit. J. Dermat. **25**:225-227, 1913.

13. Hutchinson, J.: The Study of Skin Diseases as Illustrating the Doctrines of General Pathology, Brit. M. J. **2**:163-165, 229-232, 1887; Arsenic Cancer, ibid. **2**:1280, 1887.

LUPUS ERYTHEMATOSUS

Treatment by Combined Use of Massive Amounts of Calcium Pantothenate or Panthenol® with Synthetic Vitamin E

ASHTON L. WELSH, M.D.
CINCINNATI

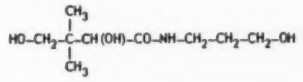
THIS REPORT deals with the results obtained in the treatment of certain phases of lupus erythematosus by the administration of combinations of various forms of vitamin E with either panthenol® (the alcohol of pantothenic acid), racemic (*dl*-) calcium pantothenate or dextrorotatory (*d*-) calcium pantothenate. Patients who had chronic discoid, disseminate discoid, or subacute disseminate lupus erythematosus were studied. Patients with acute disseminate lupus erythematosus were excluded.

Racemic calcium pantothenate has been used alone, in doses of 200 to 400 mg. daily for short periods, with benefit in the treatment of chronic discoid, disseminate discoid, and subacute disseminate lupus erythematosus.[1] Panthenol® alone, in doses varying from 0.5 to 6.0 gm. daily for periods varying from two weeks to three months has been used with improvement in all types of lupus erythematosus.[2] Vitamin E alone has been used with improvement in the treatment of lupus erythematosus.[3]

There is no report in the literature of the use of the combination of the drugs employed in this study in the treatment of patients with lupus erythematosus. In addition we could find no record of the use of these drugs in the heavy dosage or for the long intervals here employed.

DRUGS EMPLOYED

Panthenol,®[4] the alcohol corresponding to pantothenic acid, which is chemically *d*-alpha, gamma-dihydroxy-N-(3-hydroxypropyl)beta, beta-dimethylbutyramide, has the following structural formula:



Read before the Seventy-First Annual Meeting of the American Dermatological Association, Hot Springs, Va., May 25, 1951.

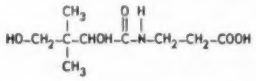
1. Goldman, L.: Treatment of Subacute and Chronic Discoid Lupus Erythematosus with Intensive Calcium Pantothenate Therapy, J. Invest. Dermat. **11**:95, 1948.

2. Goldman, L.: Intensive Panthenol Therapy of Lupus Erythematosus, J. Invest. Dermat. **15**:291, 1950.

3. Burgess, J. F., and Pritchard, J. E.: Tocopherols (Vitamin E): Treatment of Lupus Erythematosus, Arch. Dermat. & Syph. **57**:953 (June) 1948. O'Leary, P. A.: Communication to Abbott Laboratories, 1948. Burgess, J. F.: Vitamin E (Tocopherols) in the Collagenoses, Lancet **2**:215, 1948.

4. The panthenol® used in this study was supplied by Hoffman-LaRoche, Inc.

It is considerably more stable than pantothenic acid in the pH range 2 to 5.[5] It is the most active analogue of pantothenic acid hitherto described which displays vitamin activity. The medial lethal dose of panthenol[6] for mice upon oral administration was found to be approximately 15 gm. per kilogram. Panthenol,[6] given orally, is converted to pantothenic acid, as judged by the urinary excretion of the latter compound. It was administered in 0.5-gm. capsules. Calcium pantothenate was used as the dextrorotatory salt [6] and as the combination of the dextrorotatory and the levorotatory salts.[7] The formula of pantothenic acid, which is formed from beta, beta-dimethyl-alpha-hydroxybutyrolactone condensed with beta-alanine, is as follows:



The calcium salt is simply this formula with the last hydroxyl radical replaced by calcium. The dextrorotatory calcium salt of pantothenic acid, $(C_9H_{16}NO_5)_2Ca$, is the biologically active form. The levorotatory form is biologically inactive. The biological activity of the *dl*-calcium pantothenate used here was 49% that of the dextrorotatory form, as shown by the microbiological test for pantothenic acid.[8] The medial lethal dose of the synthetic dextrorotatory calcium pantothenate for mice, when given orally, was found to be approximately 10 gm. per kilogram.[9]

Pantothenic acid is essential for the nutrition of many species of animals. It is not known whether it is essential for human nutrition, although this is assumed.[10] The pantothenic acid content of normal human blood varies from 3 to 19.4 γ per 100 cc. In persons suffering from pellagra, beriberi, and riboflavin deficiency, blood levels of pantothenic acid are from 23 to 50% lower than in normal persons.[11] The requirements are increased in experimental hyperthyroidism.[12] There is some evidence that pantothenic acid may be concerned with fat and carbohydrate metabolism, particularly the rate of pyruvate oxidation in the liver.[13]

5. Rubin, S. H.; Cooperman, J. M.; Moore, M. E., and Scheiner, J.: The Physiological Availability of Pantothenyl Alcohol, J. Nutrition **35**:499, 1948.

6. Dextrorotatory salt was supplied by Benet Drug Corporation.

7. Levorotatory salt was supplied by Abbott Laboratories.

8. Skeggs, H. R., and Wright, L. D.: The Use of Lactobacillus Arabinosus in the Microbiological Determination of Pantothenic Acid, J. Biol. Chem. **156**:21, 1944.

9. Unna, K., and Greslin, J.: Toxicity of Pantothenic Acid, Proc. Soc. Exper. Biol. & Med. **45**:311, 1940.

10. (*a*) Spies, T. D.; Hightower, D. P., and Hubbard, L. H.: Some Recent Advances in Vitamin Therapy, J. A. M. A. **115**:292 (July 27) 1940. (*b*) Spies, T. D.; Stanbery, S. R.; Williams, R. J.; Jukes, T. H., and Babcock, S. H.: Pantothenic Acid and Human Nutrition, ibid. **115**:523 (Aug. 17) 1940.

11. Pearson, P. B.: The Pantothenic Acid Content of the Blood of Mammalia, J. Biol. Chem. **140**:423, 1941. Pelczar, M. J., Jr., and Porter, J. R.: Determination of Pantothenic Acid in Normal Blood and Urine by Microbiological Technic, Proc. Soc. Exper. Biol. & Med. **47**:3, 1941. Stanbery, S. R.; Snell, E. E., and Spies, T. D.: A Note on an Assay Method for Pantothenic Acid in Human Blood, J. Biol. Chem. **135**:353, 1940.

12. Drill, V. A., and Overman, R.: Increased Requirements of Pantothenic Acid and Vitamin B_6 During Experimental Hyperthyroidism, Am. J. Physiol. **135**:474, 1941.

13. Pilgrim, F. J.; Alexrod, A. E., and Elvehjem, C. A.: The Metabolism of Pyruvate by Liver from Pantothenic Acid- and Biotin-Deficient Rats, J. Biol. Chem. **145**:237, 1942.

Jürgens and Pfaltz [14] demonstrated that in rats pantothenic acid is an essential factor for the normal function of epithelial tissue. Among the effects attributed to pantothenic acid deficiency are nutritional achromotrichia,[15] dermatitis,[16] gastritis, enteritis, and ulcers of the intestinal tract,[17] hemorrhagic necrosis of the adrenal glands,[18] hemorrhagic degeneration of the testes [18] and kidneys,[17a] nerve degeneration,[19] and inhibition of growth.[20] In humans pantothenic acid seems to be combined with riboflavin [21] and inositol metabolism.[22] Folic acid and biotin may be essential for the utilization of pantothenic acid.[23] Pantothenic acid deficiency in experimental animals reduces considerably the phagocytic power of the blood.[24] Pantothenic acid analogues have an antibacterial action.[25]

14. Jürgens, R., and Pfaltz, H.: Entzündliche Erkrankungen der Respirationsorgane bei Ratten infolge von Pantothensaüremangel, Ztschr. Vitaminforsch. **14**:243, 1943.

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16. Williams, R. J., and others: Pantothenic Acid: III. Analysis and Determination of Constituent Groups, J. Am. Chem. Soc. **61**:454, 1939; IV. Formation of beta-Alanine by Cleavage, ibid. **61**:1421, 1939. Jukes, T. H.: Pantothenic Acid and the Filtrate (Chick Antidermatitis) Factor, ibid. **71**:975, 1939; Pantothenic Acid Requirement of the Chick, J. Biol. Chem. **129**:225, 1939. Weinstock, H. H., Jr.; Arnold, A.; May E. L., and Price, D.: Biologic Activity of Synthetic Pantothenic Acid, Science **91**:411, 1940.

17. (*a*) Schaefer, A. E.; McKibbin, J. M., and Elvehjem, C. A.: Pantothenic Acid Deficiency Studies in Dogs, J. Biol. Chem. **143**:321, 1942. (*b*) McIlwain, H.: Bacterial Inhibition by Metabolite Analogues: Analogues of Pantothenic Acid, Biochem. J. **36**:417, 1942.

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19. Sure, B.: Dietary Requirements for Fertility and Lactation: XXX. Role of *p*-Aminobenzoic Acid and Inositol in Lactation, Science, **94**:167, 1941. Norris, L. C., and Ringrose, A. T.: The Occurrence of a Pellagrous-Like Syndrome in Chicks, ibid. **71**:643, 1930. Phillips, P. H., and Engel, R. W.: Some Histopathologic Observations on Chicks Deficient in Chick Antidermatitis Factor or Pantothenic Acid, J. Nutrition **18**:227, 1939.

20. Schaeffer, McKibbin, and Elvehjem.[17a] McElroy, L. W., and others: On the Porphyrin Nature of the Fluorescent "Blood Caked" Whiskers of Pantothenic Acid-Deficient Rats, Science **94**:467, 1941.

21. Pennington, D.; Snell, E. E., and Williams, R. J.: Assay Method for Pantothenic Acid, J. Biol. Chem. **135**:213, 1940.

22. Woolley, D. W.: Relationship of Pantothenic Acid and Inositol to Alopecia in Mice, Proc. Soc. Exper. Biol. & Med. **46**:565, 1941.

23. Wright, L. D., and Welch, A. D.: The Role of "Folic Acid" and Biotin in the Utilization of Pantothenic Acid by the Rat, Science **97**:426, 1943.

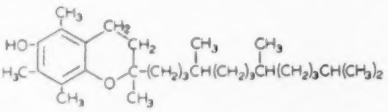
24. Cottingham, E., and Mills, C. A.: Influence of Environmental Temperature and Vitamin-Deficiency upon Phagocytic Functions, J. Immunol. **47**:493, 1943.

25. McIlwain.[17b] McIlwain, H.: Bacterial Inhibition by Metabolic Analogues: Pantoyltaurine; Antibacterial Index of Inhibitors, Brit. J. Exper. Path. **23**:95, 1942. Barnett, J. W., and Robinson, F. A.: Analogues of Pantothenic Acid, Biochem. J. **36**:357, 1943.

Spies and his associates [10b] administered varying amounts of sodium and calcium pantothenate to 15 subjects, and observed that 100 mg. of either salt may be injected intravenously without causing any significant change in blood pressure, pulse, temperature, or respiration, or any other noticeable reaction.

Studies by Unna and Greslin [9] on the toxicity of synthetic dextrorotatory calcium pantothenate caused the authors to conclude that calcium pantothenate, like the other members of the vitamin B complex, is a substance of extremely low toxicity. Excessive large doses produce death by respiratory failure in mice and rats, but prolonged feeding of sublethal doses fails to produce toxic manifestations. These facts indicate that an excess of pantothenic acid is either rapidly destroyed or excreted. In view of the foregoing investigations and many others, it will be seen that there is no basis for stating a proper dose of pantothenic acid or its salts.

Vitamin E was used as the natural mixed tocopherols and as the synthetic *dl*-alpha-tocopherol acetate (ephynal acetate®).[26] The structural formula of the alpha-tocopherol is



Beta-, gamma- and delta-tocopherols are isomers, possessing one less methyl group than alpha-tocopherol in the aromatic nucleus. Alpha-tocopherol has proved to be most effective, biologically. The dextrorotatory form of the tocopherols and the tocopherol acetate esters are much more active biologically than the racemic forms. Dextrorotatory alpha-tocopherol acetate is the most active form now known. Ephynal acetate® is the acetate ester of racemic alpha-tocopherol.

One of the striking chemical properties of vitamin E is its activity as an antioxidant.[27] It has a protective or "sparing" action in preventing the oxidation of vitamin A and carotene.[28] It also has an antidystrophic action on muscle tissue.[29]

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26. The ephynal acetate® used in this study was supplied by Hoffmann-LaRoche, Inc.

27. Vitamin E as a Physiological Antioxidant, Nutrition Rev. **3**:17, 1945.

28. Krakower, C., and Axtmayer, J. H.: Effect of Alpha-Tocopherol on Lesions of Skeletal Muscles in Rats on Vitamin A Deficient Diets, Proc. Soc. Exper. Biol. & Med. **45**:583, 1940. Moore, T., and Davis, A. W.: Interaction of Vitamins A and E, Nature **147**:794, 1941. Shantz, E. M.; Cawley, J. D., and Embree, N. D.: Anhydro ("Cyclized") Vitamin A, J. Am. Chem. Soc. **65**:901, 1943. Hickman, K. C. D.; Kaley, M. W., and Harris, P. L.: Convitamin Studies: II. The Sparing Action of Natural Tocopherol Concentrates on Vitamin A; III. The Sparing Equivalence of the Tocopherols and Mode of Action, J. Biol. Chem. **152**:303, 313, and 321, 1944.

29. (*a*) Pappenheimer, A. M.: Certain Nutritional Disorders of Laboratory Animals Due to Vitamin E Deficiency, J. Mt. Sinai Hosp. **7**:65, 1940. (*b*) Martin, A. J. P., and Moore, T.: Some Effects of Prolonged Vitamin E Deficiency in the Rat, J. Hyg. **39**:643, 1939. (*c*) Goettsch, M., and Pappenheimer, A. M.: Nutritional Muscular Dystrophy in Guinea Pig and Rabbit, J. Exper. Med. **54**:145, 1931. (*d*) Evans, H. M., and Burr, G. O.: Development of Paralysis in the Suckling Young of Mothers Deprived of Vitamin E, J. Biol. Chem. **76**:273, 1928. (*e*) Moore, T., and Wang, Y. L.: The Fluorescence of the Tissues in Avitaminosis E, Proc. Biochem. Soc., Biochem. J., 1943, vol. 37, p. 1. (*f*) Kaunitz, H., and Pappenheimer, A. M.: Oxygen Consumption in Vitamin E Deficiency, Am. J. Physiol. **138**:328, 1943.

Vitamin E has been reported to have some action on both male and female gonads,[30] on other endocrine glands,[31] on nervous tissues,[32] on muscles,[33] on vessels,[34] and on growth.[35] The recommended dosage of vitamin E varies from 10 mg. to 600 mg. daily for the multiple purposes for which it has been used. There is some slight and indirect evidence that vitamin E can be toxic.[36] Vitamin B increases tolerance for vitamin E.[37] Rancid fats destroy vitamin E.[38]

30. Martin and Moore.[29b] Evans and Burr.[29d] Kaunitz and Pappenheimer.[29f] Evans, H. M.; Burr, G. O., and Althausen, T. L.: The Antisterility Vitamin Fat Soluble E, Memoirs of the University of California, Vol. 8, Berkeley, University of California Press, 1927. Pappenheimer, A. M., and Schogoleff, C.: The Testis in Vitamin E-Deficient Guinea Pigs, Am. J. Path. **20**:239, 1944. Barrie, M. M. O.: The Effect of Vitamin E Deficiency in the Rat: I. Duration of Gestation; II. Lactation; III. Fertility in the Female, Biochem. J. **32**:1467, 1474, and 2134, 1938; V. Uterine Changes in Chronic Deficiency, ibid. **37**:523, 1943. Bacharach, A. L., and Allchorne, E.: Investigations into the Method of Estimating Vitamin E: Further Observations on Vitamin E Deficiency and Implantation, ibid. **32**:ii, and 1298, 1938. Mason, K. E.: Differences in Testis Injury and Repair After Vitamin A Deficiency and Inanition, Am. J. Anat. **52**:153, 1933.

31. (*a*) Drummond, J. C.; Noble, R. L., and Wright, M. D.: Studies in the Relationship of Vitamin E (Tocopherols) to the Endocrine System, J. Endocrinol. **1**:275, 1939. (*b*) Barrie, M. M. O.: The Relation of Vitamin E to the Anterior Lobe of the Pituitary Gland, Lancet, **2**:251, 1937. (*c*) Nelson, W. O.: Studies on Anterior Hypophysis: The Anterior Hypophysis in Vitamin E-Deficient Rats, Anat. Rec. **56**:241, 1933. (*d*) Kepinov, L.: Les vitamines A et E, agents excitants de la sécrétion de l'hormone glycogénotrope du lobe antérieur de l'hypophyse, Compt. rend. Acad. sc. **210**:188, 1940. (*e*) Tonutti, Von E.: Über die Nebennierenrinde bei Vitamin E-freier Ernährung, Ztschr. Vitaminforsch. **13**:1, 1943.

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33. Burr, G. O.; Brown, W. R., and Moseley, R. L.: Paralysis in Old Age in Rats on a Diet Deficient in Vitamin E, Proc. Soc. Exper. Biol. & Med. **36**:780, 1937. Mackenzie, C. G.: Cure of Repeated Attacks of Nutritional Muscular Dystrophy in the Rabbit by Alpha-Tocopherol, ibid. **49**:313, 1942. Gullickson, T. W., and Calverley, C. E.: Cardiac Failure in Cattle on Vitamin E-Free Rations as Revealed by Electrocardiograms, Science, **104**:312, Oct. 4, 1946. Martin, G. J., and Faust, F. B.: The Heart in Avitaminosis E, Exper. Med. & Surg. **5**:405, 1947.

34. Shute, E. V.; Vogelsang, A. B.; Skelton, F. R., and Shute, W. E.: The Influence of Vitamin E on Vascular Disease, Surg., Gynec. & Obst. **86**:1, 1948.

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36. Weissberger, L. H., and Harris, P. L.: Effect of Tocopherols on Phosphorus Metabolism, J. Biol. Chem. **151**:543, 1943. Shute, E.: A Reply to Recent Criticisms of the Theory of a Relationship Between Vitamin E and the Oestrogens, J. Endocrinol. **2**:173, 1940. Bicknell, F.: Vitamin E in the Treatment of Neurological Conditions, in The Vitamins in Medicine, ed. 2, New York, Grune & Stratton, Inc., 1946, p. 767.

37. Bicknell, F.: Amyotrophic Lateral Sclerosis and Progressive Muscular Atrophy, in The Vitamins in Medicine, ed. 2, New York, Grune & Stratton, Inc., 1946, p. 768.

38. Mattill, H. A.: Muscular Dystrophy in Rabbits and the Auto-Oxidation of Animal Fats, Proceedings of the Seventh Annual Meeting of the American Institute of Nutrition, J.

(*Footnote continued on next page*)

TREATMENT PROGRAM

When this study was begun, patients with lupus erythematosus were treated with *d*-calcium pantothenate (100-mg. capsules) alone. The original dosage varied from 0.5 gm. to 2.0 gm. daily. Some improvement was noted. Vitamin E, in the form of natural tocopherols (100-mg. capsules), was then added to the therapeutic program. The original dosage was 300 mg. daily. The dosage of *d*-calcium pantothenate was increased to 3 gm. daily, and the dosage of the natural tocopherols to 400 mg. daily. More rapid improvement was noted in patients treated at once with this higher dosage schedule than in those who started with the lower dosages. Patients who had improved for a time and then remained stationary on the lower dosage schedule began to progress favorably when put on the higher dosage schedule.

Panthenol® was then obtained for use of patients who had lupus erythematosus. At first, this was supplied in 150-mg. capsules, but later in 0.5-gm. capsules. In the early use of this agent, the daily dose was started at 2.0 gm. and slowly increased every two or three weeks to 8 to 12 gm. In later patients, the starting daily dosage was 4.0 gm., and the dosage was increased rapidly over two or three weeks to the 10-to-12-gm. level. *dl*-Calcium pantothenate became available in 0.5-gm. capsules, and we proceeded to use it in the same manner as panthenol.® Ephynal acetate® was then substituted for the natural tocopherols in the treatment schedule. This drug was supplied in 100-mg. capsules. Treatment was started with 400 to 600 mg. of ephynal acetate® daily, and the dosage was rapidly increased to 800 to 1,000 mg. daily.

Many of the patients treated with panthenol® or *dl*-calcium pantothenate with ephynal acetate® had already been taking *d*-calcium pantothenate and natural tocopherols. In order to maintain an uninterrupted treatment program, patients who started treatment with panthenol® were given *d*-calcium pantothenate or *dl*-calcium pantothenate when supplies of panthenol® were short. Conversely patients who began with *dl*-calcium pantothenate or *d*-calcium pantothenate were given panthenol® when supplies of these "starting" drugs were short. Patients were asked to resume natural tocopherols when supplies of ephynal acetate® were short. Consequently, these patients were treated with some source of pantothenic acid and some form of vitamin E for long intervals, with few interruptions.

CLINICAL MATERIAL STUDIED

Forty-two patients[39] who had lupus erythematosus were treated with the above drugs in various doses. Of these patients, 24 had chronic discoid, 11 had disseminate discoid, and 7 had subacute disseminate lupus erythematosus. Ten patients either disappeared from observation before adequate treatment could be

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Nutrition, 1940, Vol. 19, p. 13, Mattill, H. A.: Vitamin E, J. A. M. A. **110**:1831 (May 28) 1938. Cummings, M. J., and Mattill, H. A.: The Auto-Oxidation of Fats with Reference to Their Destructive Effect on Vitamin E, J. Nutrition **3**:421, 1931. Mackenzie, C. G.; Levine, M. D., Rabbit by Alpha-Tocopherol in the Absence of a Water-Soluble Factor, ibid. **20**:399, 1940. and McCollum, E. V.: The Prevention and Cure of Nutritional Muscular Dystrophy in the Mackenzie, C. G., and others: Uncomplicated Vitamin E Deficiency in the Rabbit and Its Relation to the Toxicity of Cod Liver Oil, ibid. **21**:225, 1941.

39. Two of these patients were treated in the department of dermatology and syphilology of the University of Cincinnati at Cincinnati General Hospital.

given, or had so many lengthy interruptions in the program that the treatment course was considered wholly inadequate and unsatisfactory. These 10 patients are therefore not included in the following appraisal of the treatment program outlined above. Of the 32 remaining patients who are included in this report, 17 had chronic discoid, 9 had disseminate discoid, and 6 had subacute disseminate lupus erythematosus. Twenty-three of this group had had previous treatment for lupus erythematosus, including gold preparations, bismuth, liver, oxophenarsine (mapharsen®) hydrochloride and sodium *p*-aminobenzoate. Some of these had had treatment for many years. The remaining nine patients had had no previous treatment for lupus erythematosus.

Of patients with the chronic discoid type many had had the disease from 9 to 29 years. Some already had considerable amounts of disfiguring scar-

TABLE 1.—*Treatment of Patients Who Had Chronic Discoid Lupus Erythematosus*

Case No. and Initials	Sex	Duration of Disease, Yr.	Previous Treatment	Duration of This Treatment, Mo.	*d*-Calcium Pantothenate, Gm.	*dl*-Calcium Pantothenate, Gm.	Panthenol,® Gm.	Natural Tocopherols, Gm.	Ephynal Acetate,® Gm.	Per Cent of Clearing	Complications of Treatment
1, J. G.	F	8	Yes	29	904.3	100.0	1,790.5	269.5	48.3	95	None
2, T. J. G.	M	9	Yes	21	562.8	.....	3,169.5	89.4	139.4	100	G. I.*
3, E. H.	F	10	Yes	20	1,926.0	68.4	46.5	285.6	138.6	100	None
4, E. H. H.	F	9	Yes	36	431.0	.....	2,073.4	141.5	135.5	99	None
5, H. J.	F	25	Yes	24	76.8	.....	3,122.6	123.9	163.5	85	None
6, L. L.	M	4.8	Yes	10	.....	.....	1,777.0	.....	165.2	85	None
7, R. I. R.	M	11	No	36	477.2	168.0	20.0	.....	53.0	75	G. I.*
8, R. R.	M	29	Yes	24	374.0	200.0	2,412.3	86.8	225.0	90	None
9, L. S.	F	6	Yes	30	1,254.0	.....	1,417.0	8.8	85.2	80	None
10, M. S.	F	2	No	17	1,271.2	.....	1,225.0	30.8	146.4	90	None
11, T. S.	F	10	Yes	12	.....	72.0	873.6	.....	70.2	70	None
12, L. T.	F	8	No	22	799.6	.....	100.7	182.7	.....	100	None
13, L. J. von W.	F	10	Yes	36	1,519.8	150.0	1,166.0	120.6	.....	95	None
14, W. R. W.	M	1.3	No	17	731.7	.....	1,003.0	.....	79.0	80	None
15, D. Z.	F	2	No	30	1,255.8	10.0	.....	153.2	.....	100	None
16, H. W.	M	9	Yes	14	239.4	.....	30.0	75.0	.....	70	None
17, E. H. W.	F	6	Yes	16	336.8	.....	.....	39.9	.....	100	None

* Transient gastric distress from panthenol.®

ring. Several had heavy, markedly infiltrated, and hyperkeratotic lesions. Five patients, who had chronic discoid lupus erythematosus when the above treatment was started had experienced in the past episodes of the disseminate discoid type. Four with the disseminate discoid type had subjective systemic symptoms consisting of fatigue, anorexia, arthralgia, and weight loss, as well as objective systemic symptoms consisting of low white blood cell count, relative and absolute lymphocytosis, reversed ratio of albumin to globulin, false-positive serologic reactions, etc. The duration of the disease in patients who had disseminate discoid lupus erythematosus (Table 2) and in patients who had subacute disseminate lupus erythematosus (Table 3) represents the total interval of the disease in these patients, and not just the duration of the attack present when this form of treatment was instituted. Some of the patients in each group had several episodes over a period of years.

The duration of treatment by the combined use of the drugs studied, as indicated in the tables, does not represent continuous treatment interval in some of

these patients. In many instances, a good part of the early course of treatment consisted in the use of very small doses of the drugs used. In some patients the maximum dosage schedule was employed for only the last few months of the treatment course. The shortest treatment period in the series was two months. The longest treatment period in the series was three years.

In patients in whom treatment was interrupted the disease ceased to progress favorably and, if treatment was stopped for too long, relapsed in the old sites, and in some instances new lesions developed. New lesions developed in five patients while they were under treatment with the various combinations of vitamin E and

TABLE 2.—*Treatment of Patients Who Had Disseminate Discoid Lupus Erythematosus*

Case No. and Initials	Sex	Duration of Disease, Yr.	Previous Treatment	Duration of This Treatment, Mo.	*d*-Calcium Pantothenate, Gm.	*dl*-Calcium Pantothenate, Gm.	Panthenol,* Gm.	Natural Tocopherols, Gm.	Ephynal Acetate,* Gm.	Per Cent of Clearing	Complications of Treatment
1, F. B.	M	16.5	Yes	20	258.0	11.0	3,566.0	250.5	85.2	95	G. I.*
2, D. McP.	M	3	No	26	126.8	.....	787.0	.....	75.1	100	None
3, J. M.	M	10	Yes	17	421.5	.....	1,927.0	119.8	146.9	75	None
4, A. M.	F	6	Yes	2	.....	385.0	.....	.....	15.8	80	None
5, B. T.	F	7	Yes	34	1,051.6	2,120.0	.....	43.3	215.3	85	None
6, W. T.	M	2	Yes	10	149.0	.....	1,161.0	.....	175.9	90	None
7, J. R.	F	1	No	8	.....	77.0	137.0	.....	11.4	75	G. I.*
8, A. Y.	F	7	Yes	10	.....	.....	1,336.5	126.4	.....	100	None
9, C. B.	F	7	No	18	423.0	.....	.....	72.5	.....	100	None

* Transient gastric distress from panthenol.*

TABLE 3.—*Treatment of Patients Who Had Subacute Disseminate Lupus Erythematosus*

Case No. and Initials	Sex	Duration of Disease, Yr.	Previous Treatment	Duration of This Treatment, Mo.	*d*-Calcium Pantothenate, Gm.	*dl*-Calcium Pantothenate, Gm.	Panthenol,* Gm.	Natural Tocopherols, Gm.	Ephynal Acetate,* Gm.	Per Cent of Clearing	Complications of Treatment
1, M. A.	F	0.5	Yes	12	.....	240.0	1,928.0	.....	18.3	100	None
2, M. G.	F	1.5	No	22	.....	.....	1,820.5	.....	149.2	95	None
3, B. H.	F	28	Yes	12	30.0	1,947.0	269.0	14.4	213.4	95	None
4, O. L.	F	6	Yes	27	1,673.0	.....	816.0	254.8	70.4	95	None
5, H. T.	F	0.5	No	8	.....	200.0	1,701.0	.....	130.8	99	None
6, V. D.	F	8	Yes	5	199.8	.....	.....	.....	18.0	100	None

one or more of the pantothenic acid radicals. However, such lesions were short-lived and faded out before existing older lesions were completely controlled. Arthralgias developed in six patients while under the above treatment. In each of these patients response of the arthralgia was prompt when sodium salicylate was added to the treatment schedule. In each patient exhibiting increased sedimentation rate, reversed ratio of albumin to globulin, false-positive serologic reactions, leukopenia, relative or absolute lymphocytosis, or albuminuria, reversion of these factors to normal was produced after a variable interval with the above treatment program.

It will be noted in the tables that improvement is recorded in all of the patients who were treated by the combined use of vitamin E and one or more of the pantothenic acid derivatives. Some recovered completely. Many of the others are nearly completely recovered and still under treatment. The response to treat-

ment was best and most rapid in the group with the subacute disseminate type. The group with the disseminate discoid type was next, and that with the chronic discoid type was poorest in response. In the group with the subacute disseminate type improvement was usually noted in three weeks; in the group with the disseminate discoid type, in two months, and in the group with the chronic discoid type, in four months.

Not included in the tables were eight patients with lupus erythematosus (six with chronic discoid, one with disseminate discoid, and one with subacute disseminate lupus erythematosus) who were treated with *d*-calcium pantothenate alone. The dose varied from 2 to 3 gm. daily. There was improvement, but no instance of complete recovery in any patient except the one who had the subacute disseminate type.

COMPLICATIONS ARISING FROM TREATMENT

There were no untoward complications arising from this treatment program except for transient nausea or other slight gastric upset. These symptoms occurred in only a few patients, and usually from the panthenol.[8] In these patients, either *dl*- or *d*-calcium pantothenate was then used instead of panthenol.[8] No patient was found who could not take, without reaction, one of the three pantothenic acid derivatives studied. No abnormalities in blood cells, blood chemistry, urine, or blood pressure were noted in patients who were kept on the above treatment program for long intervals. *d*-Calcium pantothenate alone was given to several hundred patients who had various dermatoses, in dosages varying from 0.3 gm. to 3 gm. daily over long intervals without any untoward complications.

Panthenol,[8] or *dl*-calcium pantothenate,[7] or d-calcium pantothenate together with natural tocopherols or ephynal acetate[9] was given to 90 patients who had cutaneous diseases other than lupus erythematosus. The number of patients and the dermatoses comprising this group included the following:

40 psoriasis
7 dermatitis herpetiformis
6 lichen planus
6 benign transitory plaques of the tongue
5 chronic infectious eczematoid dermatitis
3 seborrheic dermatitis
3 alopecia areata
2 leukoplakia
2 neurodermatitis

Besides these, one patient was chosen from each of the following disease groups: periarteritis nodosum, vitiligo, contact dermatitis, ichthyosis, morphea, atopic dermatitis, scleroderma, chronic benign pemphigus, prurigo nodularis, epidermolysis bullosum, erythema multiforme, progressive pigmentary dermatosis, erythema perstans, aphthous stomatitis, necrobiosis lipoidica diabeticorum, and lichen sclerosis et atrophicus. These drugs were given to these patients in various combinations and dosages. In no instance was there any complication except for transient gastric distress from panthenol.[8]

It is evident in the tables that each of 15 patients took over 2,000 gm. (between 4 and 5 lb.), and that Patient 1 in Table 2 took over 8 lb. (3.6 kg.) of these pantothenic acid derivatives without untoward effect. The tables also record 11 patients each of whom took over 200 gm. of vitamin E and Patient 3 in Table 1 who took 424.2 gm. without complication.

SUMMARY

Analysis is recorded of the response to treatment of patients who had chronic discoid lupus erythematosus, disseminate discoid lupus erythematosus, and subacute disseminate lupus erythematosus by the combined use of some forms of vitamin E and one or more derivatives of pantothenic acid. Very favorable results were obtained. There were no harmful effects from treatment noted in this study.

CONCLUSIONS

I feel that the combined use, in adequate dosage, of some form of vitamin E and one or more of the derivatives of pantothenic acid here employed constitutes a safe and effective method of treatment for patients with chronic discoid, disseminate discoid, or subacute disseminate lupus erythematosus.

1219 Carew Tower.

ABSTRACT OF DISCUSSION

Dr. Albert R. McFarland, Rochester, N. Y.: I would like to discuss Dr. Welsh's very fine paper from the point of view of his concept of the mode of action of these vitamins on lupus erythematosus.

As I think back some 30 years in the past, my first impression was that lupus erythematosus was in the nature of a tuberculid. During my early days of association with Dr. John H. Stokes, he summarized his impression as that of an allergic reaction due either to a tuberculous focus or to a pyogenic focus. Following this concept, we went through a period of cautious but thorough eradication of foci of infection and a search for latent foci of tuberculosis, and also the routine use of gold salts.

Next came the period of stress upon antibacterial agents and the use of arsenic and bismuth. You will recall the paper read before this association by Dr. Richard Weiss on the use of oxophenarsine (mapharsen®) hydrochloride. A little later Dr. Burgess reported improvement in this disease by the use of large doses of vitamin E. Some other investigators were unable to duplicate Dr. Burgess' findings. An unpublished but very interesting group of cases was presented a few years ago before the general staff meeting of the Rochester General Hospital by Dr. Milton Bohrod. Dr. Bohrod presented several cases with autopsy reports in which there was a combination of periarteritis nodosa, scleroderma, and lupus erythematosus. During life all these patients complained of a great variety of symptoms, and physical findings including foci of infection, allergic conditions, disturbances of liver functions, and thyroid dysfunction. He concluded that perhaps all three of the conditions mentioned were related and might be allergic manifestations of a great variety of different pathological conditions.

Then we come to the era of corticotropin (ACTH) and cortisone. Although neither of these drugs is curative in lupus erythematosus, there is no question but that they have some influence on the course of the disease.

This brings us to the question as to what is Dr. Welsh's theory regarding the action of these vitamins. Do they simply increase the body's resistance against infection? Do they in some way influence allergic reaction? Do they perhaps alter the body's reaction to its own metabolic products, or do they have some indirect effect on the glandular system, such as the adrenals and pituitary? Perhaps it would be too much to ask of Dr. Welsh to give a complete answer to these questions, but it would be interesting to know his line of thought, or, in other words, why he picked this particular line of treatment.

The tables showing the percentage of results obtained are a very important part of Dr. Welsh's paper. The percentage of cure is much higher than by any other method we have used in the past. As I recall, many of his patients obtained 98 to 100% improvement, and I believe the lowest percentage was about 75%.

If this work can be corroborated by other investigators, and if this high percentage of cure can be obtained consistently, it will certainly be a big advance in the treatment of lupus erythematosus.

DR. CARL W. LAYMON, Minneapolis: I think that most of us are far from satisfied with our results in the treatment of lupus erythematosus. Dr. Welsh's remarks were directed toward the chronic discoid and subacute forms of the disease, and he did not deal with the acute septic or the protracted systemic types. Most of us will agree that bed rest is of distinct value in all stages of the disease. This, however, is a most difficult thing to carry out when the patient is not particularly ill. Gold, and even bismuth, in the opinion of many of us, has capabilities of doing great harm in some cases. I think that these drugs have been rather overrated in the treatment of lupus erythematosus. The treatment which Dr. Welsh utilizes apparently has safety, which is extremely important. In closing I wish that he would mention the cost of such treatment.

DR. FRANK C. COMBES, New York: Dr. Welsh has taken a new approach to the treatment of lupus erythematosus. I think it is logical and can be applied to other toxic dermatoses, especially those of the bullous type. All the dermatoses in this entire group are merely cutaneous responses to remote bacterial infections, many of which are situated in the gastrointestinal and upper respiratory tracts.

I think Dr. Welsh should be congratulated for persisting in the administration of the vitamin fractions for so long in the absence of any clinical improvement. It is interesting to philosophize on why it is necessary to administer calcium pantothenate and potassium *p*-aminobenzoic acid for two or three months before benefits are evident. I have had similar experiences, and my ideas are as follows: In all our bodies we have friendly bacteria, which we call saprophytes, and those that eventually cause us trouble and which will eventually get us all some day, which we call pathogens. There is normally a balance established between these groups. We call that "good health." We know that all bacteria require vitamins for their growth and well-being. Of course, some organisms are capable of synthesizing vitamins. This is called autosynthesis, and little is known about it. In infectious diseases and bacterial toxemias the pathogens gain ascendency over both the friendly saprophytes and the immunologic abilities of the host. Pantothenic acid as its name indicates, is an all-inclusive vitamin. Its name is derived from the Greek *pas* (all) plus *theos* (god). In other words, it is "all things to all vitamins." *p*-Aminobenzoic acid occupies a similar but not quite so important position in human nutrition. Both are the protectors of all other vitamins and possibly of unknown enzymes and trace substances necessary for life.

Now when we give these large doses of panthenol® or calcium pantothenate, we are aiding vitamin synthesis in the body, necessary for nutrition of the host, and growth of the friendly saprophytes which slowly increase in number until they are predominant. I have done some studies along these lines which are quite significant but not definite enough to draw conclusions. This method of therapy does cause changes in the bacterial flora of the bowel. It is certainly a valuable addition to our therapeutic approach to the toxic bullous dermatoses and lupus erythematosus.

DR. JACOB H. SWARTZ, Boston: My associate, Dr. Glicklich, and I have used large doses of calcium pantothenate and panthenol® in a small series of 13 patients with lupus erythematosus for the past two and one-half years. Nine of the 13 patients showed fair to good improvement. None were cured. Calcium pantothenate was found more effective than panthenol.® The dose required to obtain beneficial therapeutic results was 6 gm. daily. However, 3 gm. a day was sufficient as a maintenance dose. The results were more striking in subacute and disseminate chronic discoid lupus erythematosus.

We have encountered no significant untoward reactions even in those patients who have been treated with the drug for two years. The addition of vitamin E, not synthetic, did not produce any strikingly better therapeutic results. Recently we tried large doses of ascorbic acid, 2 gm. daily, in combination with calcium pantothenate. Ascorbic acid was tried because of the favorable therapeutic results reported by Massell in rheumatic fever (personal communication). Our series is too small to merit evaluation.

One young female patient with acute disseminated lupus erythematosus improved coincidentally with the administration of large doses of calcium pantothenate. Treatment was then reduced to a maintenance dose of 3 to 4 gm. daily. She had two relapses coincidental with the omission of the drug and improved when calcium pantothenate was resumed. Of course, the report of one case is only important when it serves as an addition to a larger series. One must be cautious in such evaluations.

We have tried calcium pantothenate for other dermatoses, including psoriasis, seborrheic dermatitis, atopic dermatitis, and for two patients with lichen planopilaris. Of 25 patients with psoriasis, 13 showed some questionable beneficial therapeutic results. The two patients with lichen planopilaris showed surprising improvement. We have encountered no beneficial effects from calcium pantothenate in the other dermatoses treated, including one patient with dermatomyositis.

Dr. Ashton L. Welsh, Cincinnati: I am grateful for the ideas for further investigations suggested by my discussors. Some of the things they mentioned are already being studied. The work is still going on, as I indicated in saying that the patients were still under treatment.

I cannot explain the mechanism of the action of the combined use of these drugs in patients who have lupus erythematosus. The theory which Dr. Combes just outlined has, in my opinion, great merit. These drugs have no direct antibacterial action; hence their effect must be produced through some action favoring the activity of the normal defense mechanisms of the body.

The work was started because we had a group of patients at the Cincinnati General Hospital and in our office practice who had had lupus erythematosus for a long time in spite of much treatment with gold, bismuth, liver, etc. Many of them had become reactive and could not tolerate these conventional procedures any longer. A search was made for some approach to treatment of this group.

Pantothenic acid, as Dr. Combes stated, seemed, if one intended to employ any vitamin at all, to be the logical choice because of its wide enzyme-protective action and its pansynergetic action on many other vitamins. Vitamin E was credited with so many separate and unrelated actions, on so many tissues, that the combination of these two agents seemed a reasonable starting combination. In addition, there were favorable reports of the use of some derivatives of pantothenic acid in patients who had lupus erythematosus, and also reports of improvement from the use of vitamin E in patients who had this disease.

One drug company was willing to give us enough of these materials to start this experiment. After we had begun the study, because of the cost of the agents used, it became necessary to interest another company also in supplying the materials, in order to get adequate supplies. Patients were switched from one company's materials to materials of another company, depending on the materials currently available. Accordingly, most of the patients had combinations of several types of the two agents used. Later, it was possible to get these materials through our own pharmacist. He was able to supply these agents, at fairly reasonable prices, by purchasing very large quantities from the manufacturers, thereby obtaining a lower price.

The high dosages of the drugs employed and the long treatment intervals were arrived at automatically. As long as the patients had lesions, the drugs were administered to them, and whenever the patients seemed to cease to progress favorably, the dose was elevated. Gradually high dosage levels were reached. It was noted that each time we did elevate the dosage, the patients again showed improvement. As long as these drugs did not produce any sign of toxic reaction, no reason for not using them in this way presented itself.

I was interested in Dr. Swartz's report of his experience with the use of calcium pantothenate and panthenol* for patients who had lupus erythematosus, but I feel that his results would have been much better had he used higher dosages. I feel that his observation that the addition of natural vitamin E did not appreciably improve the therapeutic results was due to the fact that only small quantities of vitamin E were used. I was gratified that his patients improved, as did ours, on calcium pantothenate and panthenol,* and that he attested to the safety of administration of these medications.

Dr. Laymon expressed my own feelings regarding the use of this approach in handling lupus erythematosus over the older, conventional procedures on the basis of safety of the drugs employed.

The work is still continuing. An attempt is being made to find the most effective salt of pantothenic acid in the treatment of lupus erythematosus, and also to find what form of vitamin E produces the best therapeutic result when combined with that salt. It appears, to date, that the dextrorotatory form of the calcium salt of pantothenic acid and the dextrorotatory form of the acetate ester of the alpha-tocopherol constitutes the most effective combination yet employed.

While these agents are expensive, I do not think they are beyond purchase by many patients. Many patients now under treatment are purchasing their own materials. I do not know the exact cost, at the moment.

AN ATTEMPT TO DEMONSTRATE ANTIBODIES IN ECZEMATOUS CONTACT-TYPE DERMATITIS

A Preliminary Report

GEORGE H. CURTIS, M.D.
CLEVELAND

THE SEARCH for antibodies in eczematous contact dermatitis has extended principally in three directions: demonstration of the tissue of origin, establishment of a time-route relationship between local and generalization of sensitization, and identification of the antibodies. Sulzberger [1] and Landsteiner [2] suggested that sensitivity probably originates in the epidermis, although Landsteiner felt that the introduction of allergen on or into the skin was not mandatory. Haxthausen [3] concluded that antibodies are produced by the epidermis. By surgical circumvallation of skin islands Landsteiner and Chase [4] and Rostenberg [5] indicated that a substance, probably antigen or antibody emanating from the skin, was absorbed via the lymphatics. In guinea pigs Landsteiner and Chase [6] passively transmitted generalized sensitivity by lymphocytes. Haxthausen [7] confirmed these results but was unable to demonstrate local passive transmission by lymphocytes in guinea pigs or in man. Sensitizing antibodies demonstrable by passive transfer have been

Read at the Seventy-First Annual Meeting of the American Dermatological Association, Hot Springs, Va., May 23, 1951.

From the Cleveland Clinic and the Frank E. Bunts Educational Institute, Section of Dermatology and Syphilology, Dr. E. W. Netherton, Chief.

1. Sulzberger, M. B.: Dermatologic Allergy: An Introduction in the Form of a Series of Lectures, Springfield, Ill., Charles C Thomas, Publisher, 1940, p. 18.

2. Landsteiner, K.: The Specificity of Serologic Reactions, Cambridge, Mass., Harvard University Press, 1945, p. 202.

3. Haxthausen, H.: Some Problems Concerning the Pathogenesis of Allergic Eczemas, Elucidated by Experiments on Sensitization with Dinitrochlorobenzene, Acta dermat.-venereol. **20**:257, 1939; The Pathogenesis of Allergic Eczema Elucidated by Transplantation Experiments on Identical Twins, ibid. **23**:438-457, 1943; The Occurrence of Humoral Antibodies in Allergic Eczema Investigated Through Parabiosis Experiments on Guinea Pigs, ibid. **24**:286-297, 1943-1944.

4. Landsteiner, K., and Chase, M. W.: Studies on the Sensitization of Animals with Simple Chemical Compounds: Experiments on Sensitization of Guinea Pigs to Poison Ivy, J. Exper. Med. **69**:967, 1939.

5. Rostenberg, A., Jr.: Studies on Eczematous Sensitization 1. The Route by Which Sensitization Generalizes, J. Invest. Dermat. **8**:345-355 1947.

6. Landsteiner, K., and Chase, M. W.: Experiments on Cutaneous Transfer of Cutaneous Sensitivity to Simple Compounds, Proc. Soc. Exper. Biol. & Med. **49**:688-690, 1942.

7. Haxthausen, H.: Studies on the Role of Lymphocytes as "Transmitter" of the Hypersensitiveness in Allergic Eczema, Acta dermat.-venereol. **27**:275-286, 1947.

sought for in the blood, cell-free exudates [6] and blister fluid. [8] The reports concerning the antibodies in blister fluid have been particularly contradictory.

This report is concerned with repeating the Urbach-Koenigstein technic [8] and an attempt to extract antibodies from the skin.

MATERIALS AND METHOD

Five donors, of whom three were sensitive to beryllium compounds, one was sensitive to *p*-aminobenzoic acid, and one was sensitive to 2-4 dinitrochlorobenzene, were utilized.

Passive Transfer by the Urbach-Koenigstein Technic.—Blister fluid, 0.15 to 0.25 ml., from vesicles of a fresh eczematous reaction or produced by 25% cantharides plaster in 7-to-14-day-old sites was injected intradermally into normal recipients. After a fixation period of 48 to 96 hours, patch or drop tests with the corresponding allergens in corresponding concentration were performed in the usual manner. Control tests on unprepared sites were applied in all recipients.

Passive Transfer with Protein Extracts from the Skin.—Split thicknesses of skin were obtained from each of the donors in an eczematized site 72 hours to 10 days old and in adjacent normal skin. The wet weight of the specimens ranged from 265 to 1,964 mg. Each pair of specimens was gently washed free of excess blood in 1% saline solution. Four pairs were cut into frozen sections 25 μ thick, and one pair was minced without freezing. Extraction was performed in 25 ml. of saline solution by three methods: (1) ultrasonic radiation, (2) homogenization, and (3) a combination of the two.

The supernatants were concentrated in dialyzing sacs to between 0.2 and 0.4 ml. in a current of air at room temperature. Several of the supernatants were divided into two equal parts: one part was concentrated and reserved for microelectrophoretic pattern determination and the other was reserved for passive transfer. The concentrates closely resembled blister fluid. Passive transfer of the concentrates was done in the same manner as the blister fluid.

Extraction by Ultrasonics.—The apparatus employed was an "ultrasonorator" [9] with 400, 700, 1,000, and 1,500 kc. transducers submerged in transformer oil. The maximum output was 500 watts per square inch at 2,000 volts. Round-bottom flasks of 50-ml. capacity containing the tissue sections or homogenized tissue in 25-ml. saline solution were placed in the oil so that the bottoms were 0.5 cm. from the transducers and held by clamps. One drop of ether was added just before irradiation to prevent oxidation.[10] It was found that by alternate precooling to 5 degrees C. and irradiating for one-minute periods at 400 or 700 kc. and 500 watts the temperature could be held below 25 degrees C. To determine a possible inactivating effect syphilitic and atopic sera were irradiated for a total of six minutes. In the Kahn test the titer showed a decrease of one-half, but in the Wassermann test the titer was unchanged. There were no changes in the passive transfer reactions of the atopic serum. Hence the specimens were irradiated at 400 or 700 kc. and 500 watts for a total of five minutes. During irradiation the material was thrown into a violent fountain-like ebullition, and the liquid became milky. At the end of five minutes the tissue sections collected into compact clumps.

Homogenization.—The tissue sections and minced tissue were ground in a Potter homogenizer. The mortar was cooled by a jacket of water at 5 degrees C. The tissue was ground for 20 minutes, since no intact epidermis or cells were found in stained smears or blocked sections.

Each experiment was conducted under aseptic technic, and cultures of the concentrates were sterile. The concentrates were injected within 24 hours from the beginning of an experiment.

COMMENT

The results of passive transfer by the Urbach-Koenigstein technic are listed in Table 1. According to Urbach [8] cellular antibodies are enhanced in vesicular fluid

8. Urbach, E., and Gottlieb, P. M.: Allergy, New York, Grune & Stratton, 1943, pp. 179-183.

9. The Ultrasonorator, manufactured by the Crystal Research Laboratories, Hartford, Conn., was made available through Mr. H. J. Rand of the H. J. Rand Foundation.

10. Prudhomme, R. O., and Grabar, P.: A propos de l'extraction des constituents cellulaires par les ultrasons, Ann. Inst. Pasteur **76**:460-462, 1949.

of a fresh eczematous site or from a healing site produced by cantharides plaster. A positive transfer reaction may be elicited by intradermal injection or patch test with the antigen. In one experiment (No. 6) intradermal injection of *p*-aminobenzoic acid failed to elicit an immediate or delayed reaction. Ballestero and Mom [11] reported successful passive transfer from nine persons sensitized to 2-4 dinitrochlorobenzene, using 0.05 to 0.5 ml. of blister fluid and after fixation periods of 24 to 168 hours. In transferring 0.1 ml. of blister fluid from donors sensitive to other allergens and a fixation period of 48 hours Leider and Baer [12] obtained negative results. My attempts with 0.15 to 0.25 ml. of blister fluid and 48-to-96-hour fixation periods also failed. These slight variations seem insufficient to effect the positive results of Ballestero and Mom and the failures of Leider and Baer and me.

Ultrasonic radiation is a simple and highly efficient method of disintegrating and extracting the contents of soft-walled cells and organisms and is rapidly replacing pressure and grinding methods. However, tough-walled tissue cells and organisms are resistant. I found that frequencies up to 1,500 kc. with 500 watts would not disintegrate human epithelium in 10 minutes of irradiation.[13] On the other

TABLE 1.—*Results of Passive Transfer by the Urbach-Koenigstein Technic*

Experiment, No.	Donor Sensitivity	Patch Test Reactions on Donors	Results of Patch Tests on Prepared Sites in Recipients	Results of Control Patch Tests on Recipients
1	Beryllium fluoride, 2%	4+	—	—
2	Beryllium sulfate, 2%	3+	—	—
3	Beryllium benzene sulfonate, 2%	3+	—	—
4	*p*-aminobenzoic acid powder	4+	—	—
5	2-4 dinitrochlorobenzene, 1:1,000	4+	—	—
6	*p*-aminobenzoic acid	4+	— (1% *p*-aminobenzoic acid, intradermally)	— (1% *p*-aminobenzoic acid, intradermally)

hand, the alternate positive and negative pressures that produce cavitation may possibly extract cellular fluid by the oscillating distortion of the cell walls. In the split-thickness specimens the ratio of dermis to epidermis was estimated at 2 to 1; thus most of the extract probably came from the dermis. For these reasons homogenization was employed for control purposes.

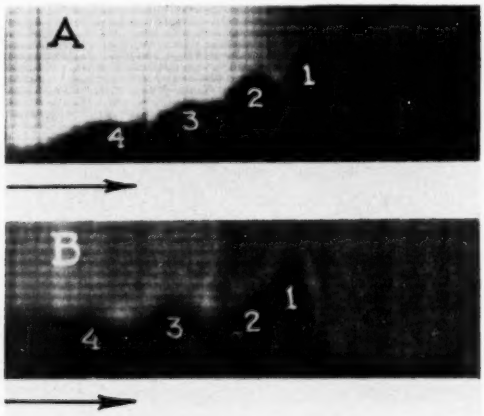
The accompanying figure shows the electrophoretic patterns of an extract (*A*) from normal skin and (*B*) from a healing eczematized site. The patterns of all extracts were similar regardless of the method of extraction. Four main components are notable. The motility of component 1 is somewhat faster than serum albumin, but the motilities of 2, 3, and 4 closely correspond to beta, alpha, and gamma globulins, respectively. In some patterns a component faster than component 1

11. Ballestero E., and Mom A. M.: Passive Transfer of Experimental Contact Dermatitis with the Urbach-Koenigstein Technic, Ann. Allergy **6**:435-439, 1945.

12. Leider, M., and Baer, R.: The Present Status of Passive Transfer Antibodies in Allergic Eczematous Contact-Type Dermatitis: Failure to Demonstrate Passive Transfer Antibodies, J. Invest. Dermat. **10**:425-433, 1948.

13. The disintegrating effect of frequencies, power, and time greater than those used in these experiments is not known to me.

was present. These patterns are similar to the findings of Holmes and Morrison [14] for dog liver and kidney extracts. The percentage of component 1 was the most constant, ranging from 42 to 46%, while fraction 2 ranged from 8 to 26%, fraction 3 from 4 to 23%, and fraction 4 from 9 to 42%. These variances could not be correlated with the methods of extraction. Had the results of passive transfer tests been positive, separation of the fractions would have been important in order to determine which fraction contained cellular antibodies.



A, electrophoretic pattern of extract of normal skin by ultrasonic radiation; *B*, pattern of extract of healing eczematized skin.

TABLE 2.—*Results of Passive Transfer with Protein Extracts of Normal Skin and Eczematized Sites*

Experiment, No.	Donor Sensitivity	Method of Protein Extraction*	Results of Patch Tests on Prepared Site of Recipient	Results of Control Patch Tests on Recipients
1	Beryllium fluoride, 2%	H H + US	..	..
2	Beryllium sulfate, 2%	H US	..	..
3	Beryllium benzene sulfonate, 2%	H US	..	..
4	*p*-aminobenzoic acid	H + US US	..	..
5	2-4 dinitrochlorobenzene	H + US US	..	..

* H—homogenization; US—ultrasonic radiation.

Results of passive transfer tests with the extracts were negative in all instances, as shown in Table 2. Several factors, such as heat, cold, and the denaturing effect of oxidation by cavitation, might have had some responsibility for the negative results. Landsteiner and Chase [6] found that antibodies in lymphocytes were destroyed at 48 degrees C. and by cold. The temperature during irradiation was maintained below 25 degrees C. To obviate the effect of freezing, in one experiment protein was extracted without freezing the tissue; however, the results were

14. Holmes, E., and Morrison, D. B.: Separation and Electrophoretic Analysis of the Proteins of Normal Dog Tissues, Federation Proc. **6**:262, 1947.

the same. Since antibodies of syphilitic and atopic sera were not destroyed, it seemed unlikely that possible antibodies in the extracted proteins were denatured by ultrasonic radiation. In view of the failures to demonstrate passive transfer antibodies in blister fluid and protein extracts, it would appear that the substance in the epidermis which reacts with the antigen (allergen) is an essential part of the chemical composition of the cellular protoplasm, and under the conditions of these experiments it could not be separated from the cells as a distinct antibody.

SUMMARY

Attempts to demonstrate passive transfer antibodies in allergic eczematous contact dermatitis by the Urbach-Koenigstein technic in persons sensitive to beryllium compounds, *p*-aminobenzoic acid, and 2-4 dinitrochlorobenzene were unsuccessful.

Protein extracts from split thicknesses of skin obtained from the donors were also used for passive transfer. A specimen of tissue was taken from normal skin and an eczematized site from each donor. Protein was then extracted by (1) ultrasonic radiation, (2) homogenization, and (3) a combination of the two. The electrophoretic pattern of the extracts showed four main components. The motility of component 1 was faster than serum albumin, but the motilities of fractions 2, 3, and 4 corresponded to beta, alpha, and gamma globulins. The denaturing effects of heat, cold, and ultrasonic radiation were controlled. The extracts were injected intradermally in normal recipients, and after fixation periods of 48 and 96 hours patch tests with corresponding allergens were performed. Results of both experimental and control tests were negative. In view of these results it would appear that, in whatever manner eczematous sensitization is acquired by the epidermis, the substance that reacts with allergen (antigen) is an essential part of the chemical composition of the cellular protoplasm and under the condition of these experiments could not be separated as a distinct antibody.

2020 E. 93d St.

Dr. George Phalen of the Orthopedic Section, Cleveland Clinic, performed the operations for obtaining the split thicknesses of skin, Dr. Georges Masson of the Research Division assisted in the preparation of the tissue for extraction, and Dr. Lena Lewis supervised the electrophoretic pattern determinations and their interpretations.

ABSTRACT OF DISCUSSION

DR. MARION B. SULZBERGER, New York: I do not know how many of you have experimented in this particular field, but all of you who have had anything to do with it must realize fully what a tremendous piece of work Dr. Curtis has performed and has reported on briefly in these few minutes. When you see the specimens there just marked on the charts with an "H" or with a "U," you must realize that each of those means a huge task in the way of preparation, testing, and controlling, and in the way of elaboration of materials and of extraction. So, this report deals with a job much greater than it appears to be from the brief and clear presentation we have just heard.

Also, this report deals with what I think is still the most common of all human allergies, one which is probably the most important and the most unequivocal of all allergies in its specificity, and one which is still the most mysterious. Why is it that in this common, well-studied disease or group of diseases which we call contact-type allergic eczematous dermatitis, which is so easily reproducible, in which we know so well the often simple chemical agents which produce the sensitization, and on which we have such good statistics and such clear-cut experimental studies, the nature of what confers this specificity of reaction is still entirely unknown?

In other words, the burden of proof is still upon those who say that antibodies exist in this type of specific sensitization. No one has had these antibodies in hand, has trapped them in a test tube, or has demonstrated their nature or actions in vitro or in vivo. Dr. Curtis' attempt is one of the many in the direction of trying to get these antibodies out and see what they are and indeed to prove their very existence. There is a long series of experimenters before him, whose names he has mentioned carefully and justly and which I need not repeat. I would, however, like to say that, by and large, most careful experimenters of the past have had negative results just as Dr. Curtis has had. In other words, the few reports which claim to have demonstrated specific passive transfer of antibodies in this form of eczematous contact-type hypersensitivity are still to be regarded as in the weak minority, and the probability is still that no one has gotten these antibodies out.

What are the reasons for this failure of previous investigators and of Dr. Curtis? He has mentioned a good many of them. First of all, perhaps these antibodies, which we are justified in supposing to be there because of the specificity and the immunologic nature of this alteration, may be so intimately associated with the structure of the cell itself, so bound to the reacting cell, that they cannot be gotten out. In other words, when you destroy the allergic cell as a living cell, you may destroy this specific property also. It may be a property bound to the nucleus, a property of a chromosome or a gene, for example.

The second possibility is that the "antibodies" are not in sufficient quantity to extract them. There may be a quantitative factor involved, or they may be so delicate as to be destroyed by all methods of extraction yet employed. Another possibility is that the antibodies do not come from the cells of the skin or the epidermis, that they do not emanate from the cells which Dr. Curtis had at all, but that they are being supplied to the skin cells by other cells. This seems to me quite possible today, in view of the work of Merrill Chase, of Haxthausen, of Sherwood Lawrence later, and now in view of more recent studies which Dr. R. L. Baer and I have been doing. All these studies indicate that the antibodies of contact dermatitis may emanate from lymphocytes or from other white cells of the blood rather than from the cells of the skin itself.

The last possibility which I will mention is that not all recipients are able to accept these antibodies. That is one possibility which Dr. Curtis did not mention, which I think is present although it is only remote. We know that antibodies which transfer other types of hypersensitivity do not sensitize all recipients equally well. Perhaps we will have to try transferring the presumptive antibodies of contact dermatitis to a very large series of subjects in order to find one whose skin cells will take them and hold them and become hypersensitive.

As I said, I believe we should all be deeply grateful to Dr. Curtis for this approach to a problem which is so baffling and so important and which requires so much further elucidation. I am particularly grateful to him for the honest effort he has made and the courage he has shown in reporting these negative results.

Dr. Clarence S. Livingood, Galveston, Texas: In experiments to be reported in the near future, we have been studying the effect of various representative contact allergens on tissue culture explants of epithelium obtained from persons who, upon patch testing, were sensitive to the contactant. We have compared these results with those obtained in other similar experiments using explants obtained from persons who were not sensitive. The contact allergens which were employed in these experiments were Rhus oleoresin, 2-4 dinitrochlorobenzene, and penicillin. We have noted no difference in the toxicity of these contact allergens for epithelial cells growing in tissue culture when the skin explants of sensitive and nonsensitive persons were compared.

Dr. George H. Curtis: I want to thank Dr. Sulzberger for his very kind and gracious pat on the back. There is very little I can say in rebuttal. If I had been able to obtain one slight glint of positivity or some evidence that there was an antibody that could be extracted from the skin, I might discuss it more fully. In regard to tissue culture in contact dermatitis, some work has been done in an attempt to demonstrate whether epidermal cells maintained contact eczematous sensitivity in tissue culture, but apparently the sensitivity is lost.

PEMPHIGUS VULGARIS

A Clinicopathologic Study

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DIFFERENTIAL diagnosis of the generalized bullous diseases is difficult, especially when individual cases are observed initially or for a short time. As Ormsby and Montgomery [1] state

> The term pemphigus was formerly applied to every disease of the skin presenting bullae. As knowledge has increased the group has been greatly reduced. The problem is not yet entirely settled, as certain types of multiform erythema and dermatitis herpetiformis are difficult to distinguish from pemphigus.

The differentiation of pemphigus vulgaris from the two bullous diseases resembling it most closely, dermatitis herpetiformis and erythema bullosum, is important from at least two viewpoints. First is that of prognosis, a fatal outcome being expected in pemphigus vulgaris. Second is that of drawing conclusions from the responses to therapeutic trials of antibiotics and hormones, such as corticotropin (ACTH) and the adrenal steroids. Obviously, a therapeutic success has entirely different and greater significance when there is certainty that the condition under treatment is definitely pemphigus and not another bullous disease resembling pemphigus.

I believe that this problem arises, as do the accompanying differences of diagnostic opinion among various observers of the same patient at the same or different times, mainly because the criteria for differential diagnosis are based chiefly on clinical observation. A comparison between the features one actually encounters in patients and the clinical features commonly accepted of the three bullous diseases in question illustrates the difficulties. The bullae themselves have no macroscopic structural features of differential value. In all three diseases there is great variation in size of the bullae. In shape the bullae may be rounded, ovoid, elongated, irregular, angular, and have pseudopods. When freshly erupted, the lesions are tense and raised in varying degree, have clear serous content, and arise from a nonerythematous base. With aging, and this period may vary widely, they become flaccid, have turbid content, and develop an erythematous halo of varying size. The duration varies for crusting and shedding, or for rupture, denudation, and repair, in the same or different patients at the same or different times. Pigmentation may occur in all, and the determining factor appears to be chronicity of the disease and ability of the patient's skin to pigment following inflammation, rather

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1. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 7, Philadelphia, Lea & Febiger, 1948.

than the type of disease present. Thus persons with light complexions may show little or no pigmentation but only irregular dusky erythema. Involvement of the mucosae may occur in all three diseases, but is more frequent, persistent, and severe in pemphigus. In pemphigus it is common for mucosal lesions to antedate the skin eruption. Itching and burning are variable symptoms. Patients with pemphigus seldom complain of pruritus, although it may occur initially or with some outbreaks. However, the burning and pain, when widespread bullae have become eroded, render the patient so miserable that this symptom predominates in pemphigus.

Because clinical observation alone, in my opinion, cannot differentiate the three major bullous diseases from one another, I have reexamined the possibility that the histologic structure of the bullae could be of differential diagnostic aid. As a result I have come to agree with those who believe that the bullae of pemphigus differ in architecture from those of erythema bullosum, dermatitis herpetiformis, and also epidermolysis bullosa. There is at present great confusion and difference of opinion in dermatologic literature and textbooks concerning the structure of bullae in the major bullous dermatoses. As a matter of definition bullae may be intradermal, subepidermal, or of mixed type.

The intraepidermal bulla has a cavity entirely enclosed within the epidermis which forms the floor, roof, and side walls or periphery. It is produced by splitting the epidermis in horizontal planes roughly parallel with the surface at varying levels, usually somewhere in the prickle-cell layer. The split may occur just above the basal layer (suprabasal), or through or just below the granular or corneous layers (subgranular or subcorneal). The subepidermal bulla is produced by the separation of the entire epidermis from the corium at the dermoepidermal junction, the accumulation of edema fluid raising the epidermis to form the cavity. Thus the floor is formed by corium only, and the roof and periphery by epidermis. The mixed type of bulla is not a primary one, but is due to degenerative and repair processes arising in both previous types. In mechanism the subepidermal bulla is produced in a manner similar to the separation of the epidermis from the dermis by moderate heat used for experimental purposes; ordinary burns produce the same effect, and this is seen in biopsies performed by electrosurgery.

Without attempting to review the entire world literature on the subject, I summarize some recent and older sources, the majority holding that no characteristic histologic structure serves to differentiate the bullae of pemphigus from those of erythema bullosum, dermatitis herpetiformis, or epidermolysis bullosa. Among those who state that the pemphigus bullae may be intraepidermal or subepidermal are the following authors. Percival and Hannay,[2] after a painstaking study of bullae from six patients with dermatitis herpetiformis, five with fatal pemphigus vulgaris, and five with erythema bullosum, stated

> The structure of some of these bullae seemed at first sight to be complicated, but, although a variety of appearances were found, they could be classified into the following three types; examples of all three types were found to occur in each of the three diseases.

These were (1) an uncomplicated subepidermal bulla, (2) a subepidermal bulla with multilocular appearance and stretching of the rete pegs, and (3) a partially

2. Percival, G. H., and Hannay, P. W.: Observations on the Structure and Formation of Bullae—I., Brit. J. Dermat. **61**:41, 1949.

subepidermal bulla, intraepidermal at the periphery and subepidermal at the center. Type 1 bullae occurred in four of their five patients with pemphigus. They concluded that the bullae were primarily subepidermal in all the three major bullous diseases. Ormsby and Montgomery,[1] MacLeod and Muende,[3] McCarthy,[4] Lever,[5] Hudelo,[6] Percival and Drennan,[7] Andrews,[8] Becker and Obermayer,[9] Allen,[10] and Montgomery and others[11] are among those who state that the bulla of pemphigus is not distinctive and may occur intraepidermally and subepidermally. MacArdle, Baumberger, and Herold[12] believe that pemphigus bullae are primarily subepidermal and secondarily intraepidermal.

The following are among those who believe or have stated that the bullae of pemphigus are primarily intraepidermal: Civatte,[13] DuPont and Pierard,[14] Lapiere, van Runckelen, and Dussart,[15] Kuhn and Iverson,[16] and Sutton and Sutton.[17] The last-named state that in pemphigus intraepithelial vesiculation occurs early and that the bullae become subcorneal when fully developed.

As a result of the cases studied, I am committed to the belief that in pemphigus vulgaris the bulla is primarily intraepidermal. Two other diseases show in their lesions a similar plane of acantholysis, keratosis follicularis and benign familial pemphigus, but clinical features and dyskeratotic changes histologically obviate their consideration in differential diagnosis. By contrast, I believe that the bullae of erythema bullosum, dermatitis herpetiformis, and epidermolysis bullosa are primarily subepidermal and cannot be differentiated from each other by unequivocal criteria in all cases. My conclusions have not been reached from a fixed point of view but have developed as the result of prolonged histologic study and clinical correlation.

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3. MacLeod, J. M. H., and Muende, I.: Practical Handbook of the Pathology of the Skin, New York, Paul B. Hoeber, Inc., 1946.

4. McCarthy, L.: Histopathology of Skin Diseases, St. Louis, C. V. Mosby Co., 1931.

5. Lever, W. F.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Company, 1949.

6. Hudelo, L.: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, Vol. 4.

7. Percival, G. H.; Drennan, A. M., and Dodds, T. C.: Atlas of Histopathology of the Skin, Edinburgh, E. & S. Livingstone, 1947.

8. Andrews, G. C.: Diseases of the Skin for Practitioners and Students, Ed. 3, Philadelphia, W. B. Saunders Company, 1946.

9. Becker, S. W., and Obermayer, M. E.: Modern Dermatology and Syphilology, Ed. 2, Philadelphia, J. B. Lippincott Company, 1947.

10. Allen, A. C.: Survey of Pathologic Studies of Cutaneous Diseases During World War II, Arch. Dermat. & Syph. **57**:31 (Jan.) 1948.

11. Montgomery, H., and others: Atlas of Dermal Pathology, Washington, D. C., Registry Press, 1948, p. 69.

12. MacArdle, R. C.; Baumberger, J. P., and Herold, W. C.: Histochemistry of Pemphigus Lesions, Arch. Dermat. & Syph. **47**:517 (April) 1943.

13. Darier, J.; Tzanck, A., and Civatte, A.: Précis de dermatologie, ed. 5, Paris, Masson & Cie, 1947.

14. DuPont, A., and Pierard, J.: Traité de dermatologie, Paris, Gaston Doin & Cie, 1938, Vol. II, Pt. 1.

15. Lapiere, S.; van Runckelen, H., and Dussart, L.: Value of Histologic Criteria in the Differential Diagnosis of Pemphigus and Dermatitis Herpetiformis, Arch. belges dermat. syph. **2**:81, 1946.

16. Kuhn, B. H., and Iverson, L.: Pemphigus Vulgaris: Clinicoanatomic Study, Arch. Dermat. & Syph. **57**:891 (May) 1948.

17. Sutton, R. L., and Sutton, R. L., Jr.: Introduction to Dermatology, Ed. 4, St. Louis, C. V. Mosby Company, 1941.

In this series of 33 cases of frank pemphigus vulgaris, I observed the patients personally, during their stay in Bellevue Hospital, at least once a week for periods of many months, in the majority until death ensued. In some patients several bullae were removed for study at different times. Biopsy blocks were sectioned entirely or in major portion and examined in series. In some, well over 100 sections were cut. A few patients were observed before 1941 when I first became interested in this problem. However, the majority of cases were followed systematically since 1946. At the beginning, lesions were removed for biopsy at random, but experience indicated that it was necessary to examine fresh bullae to obtain reliable information, since bullae were not static but changed in clinical and histologic appearance within a period of hours or days. The rate of change varied considerably among different patients and in the same patient at different times. When lesions were sparse, a new or fresh bulla could be easily discovered by the patient, nurse, resident physician, or myself. As a matter of experience, a young or early lesion was one which was clear, tense, elevated, and without erythematous halo. Conversely, a turbid and flaccid bulla with erythematous halo was rejected as unsuitable whenever there was a choice. A small lesion was preferred, and removal was *in toto* with a rim of intact skin, and rupture was avoided. Unfortunately, no mouth or other mucosal lesions were removed for study because early rupture and the site itself have so far prevented this.

I believe the following are responsible in part for the confusion and differences of opinion concerning the site of the bullae in pemphigus, erythema bullosum, dermatitis herpetiformis, and epidermolysis bullosa: (1) failure regularly to study biopsies of early lesions *in toto;* (2) incomplete sectioning of the blocks, with failure to obtain central sections, and (3) failure to recognize the changes produced by aging, erosion, and repair.

In the fresh or young bulla of pemphigus the earliest change seen is rupture of the intercellular bridges between the basal cells and the prickle cells above them, and separation between them by filling of the space with tissue fluid. A few delicate strands of cytoplasm, probably stretched intercellular bridges, still connect some of the separating basal and prickle cells. This stretching and rupture of intercellular bridges may also occur between the basal cells themselves, leading to separation laterally, so that they give the appearance of a row of tombstones or a picket fence. However, a significant fact is that the basal cells remain firmly attached on their proximal surfaces to the fibers of the corium below. By contrast, it is just at this plane that the entire basal layer is torn away from the corium in the subepidermal bulla. This is the primary point of distinction between the early intraepidermal bulla of pemphigus and the subepidermal bullae of the other diseases. Concurrently with the splitting of the epidermis, or very rapidly thereafter, the space created fills with tissue fluid and forms the bulla cavity. This study is not concerned with the mechanism whereby the fluid enters the cavity, or its composition. Whatever the physiologic mechanism, the tissue fluid does localize in the bulla and is derived from the superficial dermal vascular system after filtration into the tissue space. The presence of basal layer does not act as a barrier to the flow of tissue fluid into the cavity, the increased intercellular spaces probably acting as the points of seepage. At this early stage there are few or no inflammatory cells present in the bulla, and vasodilatation, edema, and inflammatory cell infiltration

into the subjacent corium appear to be minimal. The bulla roof is formed by the residual epidermis, that is, the distal portion not retained in the floor, and consists of most of the prickle, granular, and corneous layers. The cells are not edematous or degenerated. Frequently and almost regularly in all or some areas, there is rupture of intercellular bridges among the cells of the lower prickle-cell zone close to the main plane of acantholysis which has produced the bulla. This liberates single cells or varying-sized clumps which lie or float free in the bulla cavity. No early specific degenerative changes in the epidermal cells are discernible with the histochemical reactions at present employed in the usual staining methods. Concerning the degenerative changes described in the loosened epidermal cells in the bulla cavity, I have frequently noted them. However, I have reservations against ascribing any specific meaning to these degenerative effects, since they are variable. They may be nonspecific and due to the detached state of the cells in the bulla fluid. The liberated epidermal cells and the retention of epidermis as the floor of the bulla form the basis of Tzanck's [18] test.

A feature frequently seen is the extension of the plane of splitting of the epidermis at or close to the suprabasal level into the sides or periphery of the bulla. This is at times foreshadowed by increased intercellular edema in the same plane, without actual rupture of the stretched intercellular prickles in the peripheral and adjacent epidermis. Such potential tiny intraepidermal bullae may occur in the clinically normal-appearing skin. The plane of acantholysis is not always regularly suprabasal. The most frequent variation is a more or less irregular plane of cleavage, slightly higher in the prickle layer, which results in the bulla floor being formed by basal layer plus a few contiguous cells of the prickle layer, seldom more than three or four rows. This occurs in an irregular manner, and consequently cross sections show a floor formed by basal layer alone in some places, especially toward the periphery or edges, while in other areas it consists of basal layer plus one or more rows of prickle cells. When the epidermis is acanthotic or the rete ridges (pegs) are well developed, the plane of cleavage occurs at the usual level but may not involve the ridges. In this instance the bulla floor is formed by the epidermis of the ridges and the basal layer of the suprapapillary portions of the epidermis. The ridges or pegs thus lie below the general level of the floor and give the rough appearance of a comb, the teeth consisting of the rete pegs facing downward in the upper corium. In addition, one or more prickle-cell layers may adhere to the basal layer of the suprapapillary portions. At other times the splitting may descend into the rete ridges or pegs at or near the suprabasal level to give the floor of the bulla a wavy outline of basal cells, alone or plus some prickle cells. To some extent this preserves the original rete-ridge pattern.

Another phenomenon observed is the extension of the acantholysis into the walls of the pilosebaceous glands and orifices. This may result in a peculiar microscopic picture. A group of sebaceous cells has in a few instances been found in the cavity of the intraepidermal bulla. In these cases there is a pilosebaceous follicle lying below the bulla, and serial sections reveal that its orifice is involved

18. Tzanck, A.; Bourgeois-Gavardin, and Avon-Brunetiere, R.: Immediate Cytologic Examination in Dermatology, Ann. dermat. et syph. **8**:205, 1948, cited in The Year Book of Dermatology and Syphilology, 1948, edited by M. B. Sulzberger, Chicago, The Year Book Publishers, Inc., 1949, p. 485.

in the bulla and that the acantholysis producing the bulla has extended into the orifice wall as well as into the lobules of the sebaceous gland itself. Since the cleavage here also occurs above the basal or outer cell layer, the result is partial or complete loosening and detachment of the inner masses of sebaceous cells. It is thus possible that an entire small lobule may be liberated and float upward a short distance into the bulla cavity. This is analogous to the clumps of prickle cells liberated from the epidermis and found floating free in the bulla cavity. A less likely possibility is that the loosened clumps of sebaceous cells may be carried upward mechanically by the microtome blade. A similar extension of the cleavage into sweat ducts is far less common, since, so far, I have observed only one such instance.

Further changes in the structure of the pemphigus bulla result from a mixture of two general processes: increasing edema, inflammation, and erosion, and repair which reconstitutes the epidermis. These stages overlap and produce confusing histologic pictures. As the bulla ages, the upper corium contains more dilated small blood vessels (reflected clinically as the erythematous halo or base), edema increases, the cellular infiltrate which earlier was chiefly perivascular becomes more profuse and diffuse, eosinophiles and neutrophiles are more numerous and are found predominantly just below the floor of the bulla and in the cavity. The continued edema and inflammation cause loosening of the basal cells of the floor so that they are washed out into the bulla cavity, there to float free and to degenerate. This washing-out process may occur in irregular fashion, and in old bullae it may involve most of the floor epidermis, with the result that bare corium comes to form the floor and give the appearance of a subepidermal bulla. Careful examination of many sections in such instances is necessary to detect traces of the original epidermal floor.

With aging, the prickle and granular cells of the roof undergo degenerative changes. There is intercellular and intracellular edema, as shown by pallor and eosinophilic staining, thinning, and compression, and the nuclei become pale and ghost-like or compressed and pyknotic as in parakeratosis. Rupture of the roof may occur, either while not degenerated or later during any stage of degeneration. However, the roof may remain intact until it is fully degenerated and be shed as a desiccated, thinned, parakeratotic scale. Beneath it the epidermis may have regenerated or a new bulla may have formed.

Regeneration of the epidermis from the basal and prickle cells of the bulla floor may begin before the roof ruptures or is shed. The regrowth tends to begin in the central area of the floor and proceeds more rapidly than at the periphery. Not infrequently the original plane of acantholysis is still apparent at the periphery while active regrowth has occurred in the rest of the bulla floor. The regrowth may be uneven and irregular and may be most pronounced from the remnants of the rete ridges. Early, there may be edema and invasion by inflammatory cells of the regrowing epidermis which tends toward eosinophilic staining. New acantholysis may occur in the regenerating epidermis, giving the striking appearance of a new intraepidermal bulla below an older healing and shedding bulla (bulla under bulla). Complete restitution occurs when the granular layer is formed. By contrast, subepidermal bullae heal by regrowth of the epidermis across the original floor of

corium, starting from the periphery. The early growth takes place as slender processes of basal and prickle cells which arise from the acanthotic and rounded rete pegs which form the walls of the subepidermal bulla at this stage. Thus, regrowth appears earliest at the periphery and is most pronounced there. Later it extends over the central area, growing inward in a very irregular pattern of thin

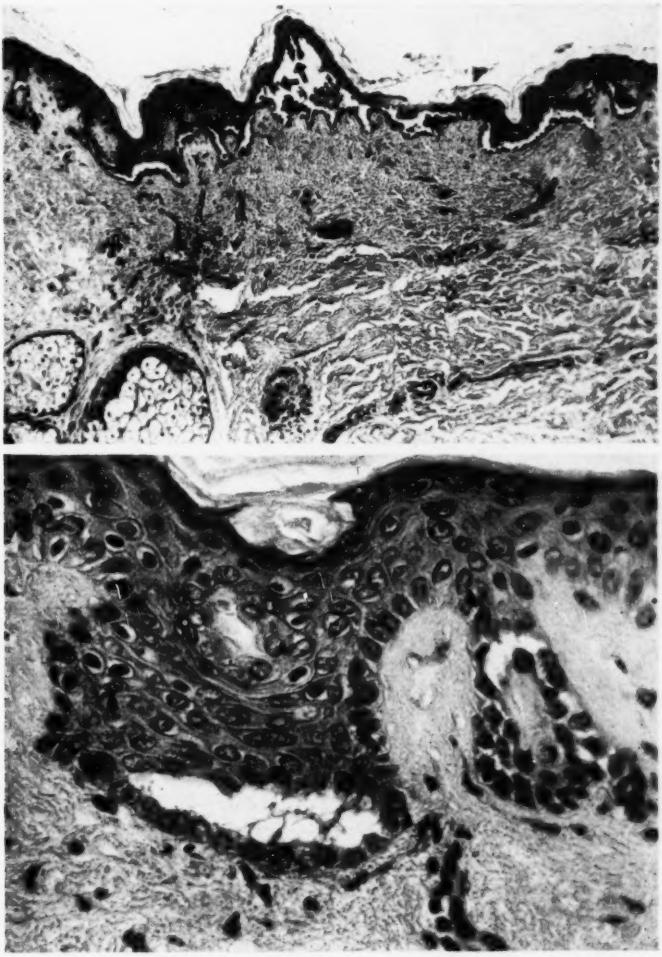

Fig. 1 (patient M. K.).—Upper, early intraepidermal bulla typical of pemphigus vulgaris produced by acantholysis at the suprabasal level with extension into the rete pegs, periphery, and adjacent epidermis. The floor is lined predominantly by basal cells; the cavity contains single and clumped free prickle cells, but very few inflammatory cells; the roof consists of the residue of the epidermis, and arrows indicate the major portions of three rete pegs on the under surface; inflammation in the subjacent corium is minimal; × 113. Lower, another section from same biopsy specimen; very early acantholysis at the suprabasal level in a single rete peg which is traversed by a sweat orifice. The epidermal cells show no demonstrable degenerative change. Note the stretched but not completely ruptured intercytoplasmic connections. The tiny cavity contains no cells. There is similar cleavage in an adjacent smaller peg; × 430.

sheets of epidermal cells. The bulla of pemphigus may take one of two paths in evolution. It may heal by regrowth from the basal and prickle cells of its floor; or the basal and prickle cells of the floor may be washed out completely, and, with rupture and degeneration of the roof, denudation may result and persist for a long time, until death ensues or until there is very slow epithelization.

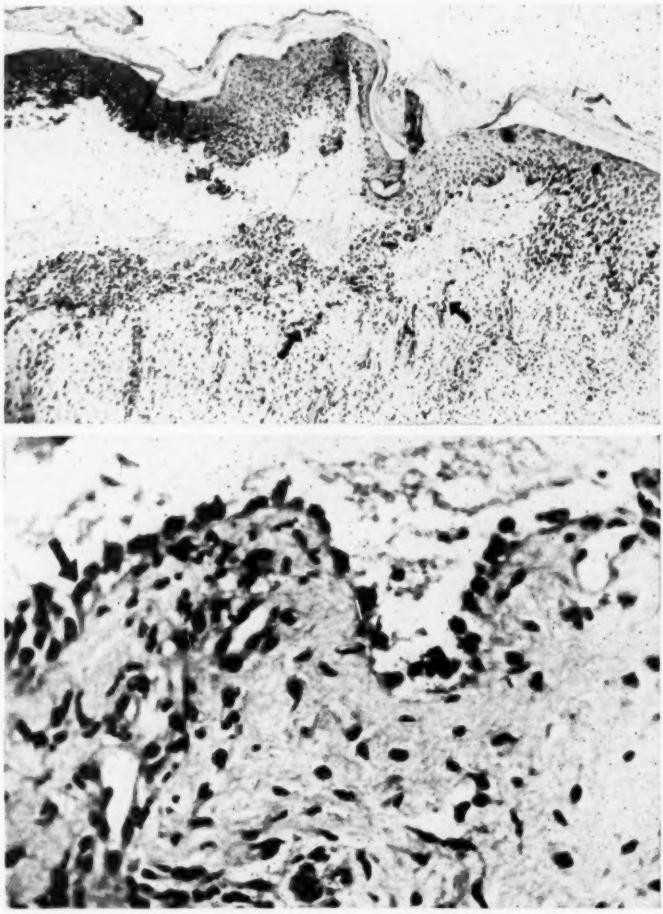

Fig. 2 (patient L. B.).—Upper, biopsy specimen of an old bulla with superficial appearance of a subepidermal bulla due to washing out of the basal layer of the edematous floor; arrows indicate remnants of basal cells in the floor; × 79. Lower, same section, × 380, showing the remnants of the basal cells of the floor outlining the contour of the papillae. Although still attached to the corium, the distal position of the nucleus and stalk-like appearance of the cytoplasm distally indicate that the basal cells are undergoing detachment (arrow); other basal cells are completely separated and afloat in the cavity.

The bullae of erythema bullosum, dermatitis herpetiformis, and epidermolysis bullosa are formed by the almost-explosive raising of the entire epidermis from the corium, caused by the pressure of the edema fluid. The epidermal cells of the roof

so formed remain coherent; their intercellular prickles are not involved in the disease mechanism, and the entire epidermis retains its integrity. The attack by the disease process is at the dermoepidermal junction so that there is rupture or solution of the denticulate processes of the proximal surfaces of the basal cells

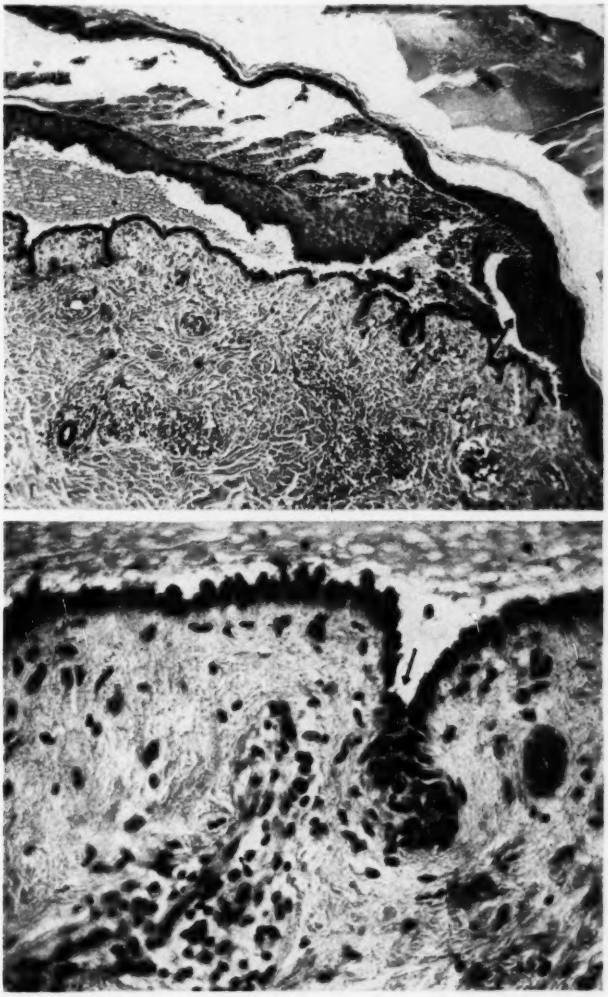

Fig. 3 (patient L. B.).—Upper, biopsy specimen of clinically fresh bulla showing phenomenon of "bulla under bulla." Uppermost are the degenerated roof and drying cavity of the original bulla; below lies the epidermal floor of the original bulla regrown to the point of granular layer formation; acantholysis in it at the suprabasal level has produced the fresh typical bulla. Note the junction of the new and old bullae at the periphery where arrows point to both old and fresh cleavages. There are perivascular foci of inflammation in the upper corium but very little in the papillary zone. Lower, same section, × 345, showing the epidermal floor of the lower fresh bulla which consists predominantly of basal cells firmly attached to the corium. An arrow points to the partial acantholysis in a rete peg. There are few inflammatory cells in the cavity and papillary corium.

which are joined to the fine connective-tissue fibers of the subjacent corium. This is sharply contrasted with the disease mechanism in pemphigus. Here, primarily, there is a solution and rupture of the intercellular bridges between the basal and adjacent prickle cells or among the prickle cells themselves, resulting in acantholysis at varying and irregular levels of stratification. The dermoepidermal junction remains primarily unaffected and results in the epidermal lining of the bulla floor.

Fig. 4.—(Patient I. Ba.). Upper, showing another instance of "bulla under bulla;" regrowth of epidermal floor of primary bulla and secondary acantholysis in it roughly at the suprabasal level, with extension into the rete pegs; washing out of some basal cells of the new floor at the periphery. Note also the suprabasal cleavage in the rete pegs of the adjacent epidermis, one of which contains a sweat orifice; × 113. (Patient R. C.) Lower, showing an aging intraepidermal bulla with thinning and degeneration of the roof centrally. The epidermis in the center of the floor has regrown to the point of granular layer formation (arrow *A*). Toward the periphery regrowth has lagged since the floor consists predominantly of basal layer (arrow *B*). Secondary acantholysis in the regrown central epidermis has produced a small focus of "bulla under bulla" (arrow *C*). This illustrates the uneven evolutionary changes of the pemphigus bulla; they are more advanced centrally and lag at the periphery; thus single sections of the same biopsy may yield interpolated clues; × 73.

This regularly occurring difference must be the microscopically visible evidence and result of a specific disease mechanism and not merely a haphazard effect. Its pathologic physiology remains to be determined.

I have described a dynamic picture of the events which take place in the formation and course of the bulla of pemphigus, and will do so for the other bullous diseases in question subsequently. It may justifiably be asked how it is possible to assume such an interpretation from the study of tissue sections which, one must

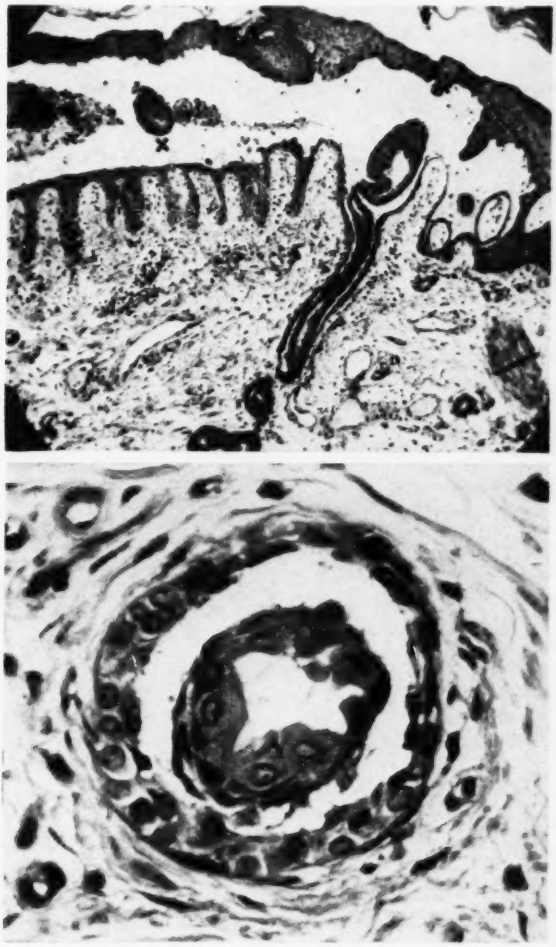

Fig. 5 (patient Y. M.).—Upper, showing the periphery of a large intraepidermal bulla. A sweat duct is seen in longitudinal section rising into the floor and cavity. Its wall has undergone cleavage at about the same level as has the contiguous epidermis, i. e., above the lower two-to-three-cell layers. This split in the duct wall extends downward into the midcorium where it is seen partially in a cross section of sweat duct just below the longitudinal section. The bulla floor is somewhat regrown except toward the periphery, where it is thinner. In the cavity at *x* is a cross section of sweat duct as well as rounded and irregular clumps of degenerating epidermal cells liberated by the acantholysis; × 72. Lower, another area of same biopsy specimen; × 535; cross section of a sweat duct with cleavage of its wall. The outer tube of cells is analogous to the basal and suprabasal layers of the surface epidermis forming the bulla floor. The outer cleft represents the bulla cavity and the inner tube of cells the roof. The cleavage is similar to that which produces the typical intraepidermal bulla of pemphigus. Note at the lower pole the incomplete separation between the cells of the outer and inner tubes.

freely admit, are static and represent bits of reality fixed in time and place. It is impossible to follow the progress of any single bulla, histologically, from the beginning to the end of its evolution. A biopsy specimen of a bulla or other lesion can show only how it looks at the moment of removal. It cannot tell us the exact events which preceded or would have followed. Nevertheless, assuming logically that the

Fig. 6 (patient I. C.).—Section showing close to a large typical intraepidermal bulla a similar tiny one in the cavity of which lies a clump of liberated sebaceous cells. Directly below in the mid and lower corium can be seen a pilosebaceous follicle. Arrows in both the sebaceous gland and the hair follicle components show cleavage at about the same analogous levels as in the surface epidermis. Consecutive sections demonstrated the continuity of relationships between the gland and the small bulla; × 111.

lesions of a disease which appear clinically alike throughout their evolution will show similarly varying histologic changes, biopsy specimens of different lesions in the same patient at different stages in development should offer such evolutionary evidence as to permit a correct deduction of the histologic course of events. Thus

a series of biopsies in the same patient permits logical interpolations. This is basically the same method of deduction employed in the interpretation of a series of gastrointestinal roentgenographs. It is not more indirect than the information founded on the photographic evidence of the tracks made in the cloud chamber by electrons and other particles. Further, the sectioning of an entire bulla gives a series of changes which, on rather simple reasoning and the study of many lesions in the same manner, lead to conclusions that progressive changes must have led to the appearances observed.

COMMENT

Most, but not all, of the cases in this report were included in the broad survey by Combes, Canizares, and others [19] of a larger group of patients with pemphigus. My report is an independent one in the sense that the study was initiated with the specific purpose of correlating the clinical features of the disease with its histopathology from the viewpoint of differential diagnosis from the pemphigus-like diseases. It is thus limited to those patients whom I have observed personally and for whom I have been able to carry out adequate histopathologic studies. Since a detailed summary of each of the 33 cases is impractical, I am summarizing some pertinent features of the entire group of patients.

A fatal outcome in a patient with generalized bullous disease is usually considered to favor the diagnosis of pemphigus. It is my belief that death alone is not an unequivocal proof of this diagnosis, especially in elderly patients. Two factors seem to me to have importance in the clinical differentiation of true pemphigus from pemphigus-like disease in this respect. First, the presence of a serious disease other than the bullous disease can mean that death is caused by the underlying illness rather than by the presenting bullous eruption which is not necessarily pemphigus. Or, to restate this from the opposite point of view, an ultimately fatal underlying disease may, during its course, induce an erythema bullosum reaction which resembles pemphigus. Second, if the active eruption of bullae has ceased many weeks or months prior to death, it is unlikely that the diagnosis is pemphigus, for in this disease lesions usually persist and actively appear until the end. In the 33 cases of this report, death was not principally or apparently caused by another underlying disease. Moreover, there was active eruption of lesions on the skin and mucosae at the time of demise. In only one elderly and debilitated woman did death occur when the eruptive phase was subsiding. However, in none was the skin completely free of recent lesions.

Of the 33 patients, 16 were men and 17 women. All had died by the time of writing. The duration of the disease in 29 was less than one year; in 28, less than 10 months, and in 1, just under 11 months. In only four patients did the duration exceed one year. Two women died after a duration of a little over 16 and 17 months, respectively; two men survived 22 and 37 months, respectively, after the onset of the disease. In both of the latter cases there were remissions: one remission of two months in the first, and two remissions in the second, of one year and one and one-half years, respectively. The latter patient had three attacks which, in sequence, lasted six months, six weeks and five weeks. Thus in 29 cases, or 87%, the total duration was less than one year, while 4 patients, or 13%, survived more

19. Combes, F. C., and Canizares, O.: Pemphigus Vulgaris, a Clinicopathologic Study of 100 Cases, Arch. Dermat. & Syph. **62**:786 (Dec.) 1950.

than one year. The youngest patient was 36 years, and the oldest, 80. The major distribution (24 patients) was in the fifth through the seventh decades. The interval between the onset of the disease and death varied from six weeks to 37 months, although the longest period of continued active disease was about 17 months.

Concerning clinical features, three patients at some time during the course of their illness presented more or less the appearance of pemphigus erythematosus. This consisted in patches of crusted, scaling erythema on the cheeks, nose, scalp, chest, and back in varying combination as well as lesions elsewhere. The duration of such an appearance was relatively short and resulted from the protracted crusting in patches of lesions which were originally bullous. Pronounced erythematous patches and plaques were observed in two patients. In the first patient plaques of edematous erythema were studded with small and large vesicles and resembled the lesions of erythema multiforme bullosum. This patient died after 14 weeks of his disease. In the second patient large patches of edematous erythema appeared during the final week of life while receiving cortisone. Large areas of inflamed skin were easily detached on slight pressure. The total duration of his disease was 12 weeks.

In the group at large, bullae appeared in all shapes and sizes from the very tiny to those several inches in diameter. Freshly erupted lesions had a clear content, were tense and rounded and arose on a nonerythematous base. Very rarely a bulla was seen with hemorrhagic content. The evolution toward turbidity, flaccidity, and erythematous halo varied considerably, several hours to days being required to produce changes in appearance. The stages of crusting and erosion before healing lasted many weeks in some patients but less in others, and even this varied at times for the same patient. Itching was noted in 5 of the 33 patients and was of mild or moderate degree. Usually it occurred during the early stages of the disease while the bullae were erupting. Later, when lesions were profuse and there was much crusting and erosion, pain predominated. Itching, therefore, occurred relatively seldom, in about 15% of the patients, and was neither pronounced nor prolonged.

Lesions of the mucosae (lips, mouth, and conjunctivae) preceded the appearance of bullae on the skin in 23 patients, or about 70%. The lips in two patients and the conjunctivae in one patient were involved before the mouth. Eye involvement in the form of conjunctivitis occurred in four patients, but bullae were not seen. There were no instances in which eye involvement led to destruction of the eye or blindness. The interval between the appearance of mucosal and cutaneous lesions was one month or less in 11 patients, one to three months in 5 patients, and four to eight months in 7. Thus the interval varied from several days to eight months. In eight patients, or 24%, skin lesions preceded those in the mouth by an interval varying from one or two weeks to four months. Included were two patients whose earliest lesions were on the scalp and penis, respectively. In the patient whose disease lasted the longest (37 months) and who had three separate attacks, there were no mouth lesions during the first and second episodes. However, in the third and final attack, bullae did erupt in the mouth, but only after they had appeared earlier on the skin. Lesions of the mucosae occurred initially and throughout the disease in varying degree in 31, or 94%. In only two patients were mouth or other mucosal lesions absent or never noticed.

Significant but nonspecific laboratory findings were hypoproteinemia, with or without inversion of the albumin-globulin ratio and secondary anemia. The white blood cell count varied from normal to moderate leucocytosis, the latter especially when there was a complicating infection or widespread lesions with crusting and erosion. Blood eosinophile counts above the normal were found in 17 patients. Of these, at one time or another, 7 reached a level of 11 to 23%, and 10 were between 6 and 9%. In 16 patients there was no elevation of eosinophiles in the blood. Eosinophilia of varying degree of the bulla cavity and upper corium was noted in 19 patients. In 18 patients the blood eosinophiles were normal or increased, and in 1 patient none were found. In 14 patients eosinophiles in the biopsied tissues were absent or present in insignificant number; 10 of these had a normal level or absence of blood eosinophiles, while in 4, eosinophiles were increased, in 2 reaching levels of 6 to 13 and 18%. No significance could be placed on these correlations between blood and tissue eosinophile levels, since the blood counts were not done at the same time as the biopsies. In general, however, eosinophilia of blood and tissue was neither pronounced nor always present.

CONCLUSIONS

1. Pemphigus vulgaris, excluding definitive pemphigus vegetans and foliaceus, is a bullous disease with the following clinical features: (*a*) It is invariably fatal so far as can be judged at present, with a possible reservation concerning the efficacy of corticotropin and cortisone therapy in some cases. (*b*) The duration of the disease in the large majority of patients is under one year, although in a minority it may be more than three years, continuously or with remissions. (*c*) Lesions of the mucosae appear initially and/or throughout the course of the disease in the vast majority of patients. (*d*) Itching is not an important or prominent symptom. (*e*) The disease seldom occurs in persons under 30 years old.

2. The bulla is characteristically intraepidermal, but this location is not pathognomonic. (*a*) The primary change is acantholysis or cleavage of the epidermis at, or close to, the suprabasal level, and there is extension into the rete pegs, the appendages, peripheral, and adjacent epidermis. (*b*) Epidermal cells are liberated into the cavity of the bulla, singly or in clumps. (*c*) The inflammatory reaction is secondary, variable, and not characteristic. (*d*) The processes of erosion and repair can confuse the primary intraepidermal site and structure; nevertheless, enough of the primary features may persist to be of diagnostic aid.

3. The histologic appearance of the bulla, in conjunction with the clinical picture, is at present the most reliable means of differentiating pemphigus vulgaris from the similar major bullous diseases, dermatitis herpetiformis and erythema multiforme bullosum.

67 Park Ave. (16)

LUPUS ERYTHEMATOSUS ASSOCIATED WITH PREGNANCY AND MENOPAUSE

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ACCORDING to O'Leary,[1] Kaposi in 1872 was the first to describe acute disseminated lupus erythematosus. Mook, Weiss, and Bromberg[2] in 1931 reported 13 cases, and in 1932 Madden[3] reported 9 cases of acute lupus erythematosus. Since then many authorities have written and discussed the subject of acute disseminated lupus erythematosus. Baehr and Jarcho[4] stated that 95% of the patients are female. We recently observed and treated three pregnant women who had acute disseminated lupus erythematosus which terminated fatally; therefore, we decided to survey the problem of the relationship of pregnancy to lupus erythematosus.

There are conflicting opinions regarding the relationship of pregnancy to acute disseminated, subacute disseminated, chronic disseminated, and chronic discoid lupus erythematosus. The following questions are posed. Is any particular type of lupus erythematosus prone to become worse during pregnancy? Does lupus erythematosus frequently start in pregnancy or after delivery? Does lupus erythematosus affect the pregnancy adversely? Is it advisable to terminate pregnancy in patients with acute or subacute lupus erythematosus? Does chronic discoid lupus erythematosus tend to disseminate in pregnancy or become more acute in pregnancy? Do the hormonal changes of pregnancy have a favorable effect on lupus erythematosus? The answers to these questions are of interest to the internist, the obstetrician, and the dermatologist. We have reviewed the literature and have undertaken a survey of current opinions on this subject by sending a questionnaire to 280 recognized American dermatologists requesting their opinions.

Rose and Pillsbury[5] emphasized that the acute disseminate type of lupus erythematosus almost always affects women who are in active menstrual life at the onset of the disease. The relation to ovarian function is further suggested by pre-

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1. O'Leary, Paul: Disseminated Lupus Erythematosus, Minnesota Med. **17**:637, 1934.

2. Mook, W. H.; Weiss, R. S., and Bromberg, L. K.: Lupus Erythematosus Disseminatus, Arch. Dermat. & Syph. **24**:786 (Nov.) 1931.

3. Madden, J. F.: Acute Disseminated Lupus Erythematosus, Arch. Dermat. & Syph. **25**:854 (May) 1932.

4. Baehr, G., and Jarcho, S.: Lupus Erythematosus Disseminatus from the Point of View of Internal Medicine, Oxford Medicine **4**:44 (66-1), 1950.

5. (*a*) Rose, E., and Pillsbury, D. M.: Acute Disseminated Lupus Erythematosus: A Systemic Disease, Ann. Int. Med. **12**:951, 1939; Lupus Erythematosus (Erythematodes) and Ovarian Function: Observations on a Possible Relationship, with Report of 6 Cases, Ann. Int. Med. **21**:1022, 1944.

menstrual accentuation of cutaneous lesions reported by some patients and by favorable response to ingestion of testosterone propionate in an occasional patient. Montgomery [6] stated that Curtis observed only temporary improvement following oophorectomy. Montgomery and his colleagues have had similar experiences in two cases. After a review of various types of disseminate lupus erythematosus associated with pregnancy which were seen at the Mayo Clinic, O'Leary stated in a discussion of Baehr and Pollack's paper [7] that "therapeutic castration of women who have disseminate lupus erythematosus has been valueless" in his experience. Baehr and Pollack also stated that treatment of lupus erythematosus with testosterone propionate or castration in females has not materially altered the course of the disease. They regard the female predominance as merely representing sex predisposition similar to the male predominance seen in thromboangiitis obliterans. Fromer [8] reported favorable therapeutic response to injections of testosterone.

Michelson [9] stated that suppression of ovarian function has not been beneficial in a large enough percentage of patients to warrant advocating oophorectomy in the treatment of lupus erythematosus. According to Montgomery, the predominance

QUESTIONNAIRE

A. Acute lupus erythematosus (associated with systemic signs or symptoms).
   1. Pregnancy—Effect of pregnancy on the acute lupus erythematosus.
      a. Number of cases?
      b. Number of maternal deaths?
      c. If not fatal, final outcome?
      d. Effect in subsequent pregnancies?
   2. Effect of acute lupus erythematosus on pregnancy.
      a. Number of fetal deaths?
   3. How many cases of acute lupus erythematosus have you seen starting after menopause?

B. 1. Do you think that pregnancy has any effect on chronic discoid lupus erythematosus or disseminated lupus erythematosus (not acute)?
   2. If so, kindly mention the approximate number of cases and what effect?

of acute disseminate lupus erythematosus among women has been attributed to ovarian dysfunction and to pregnancy, and in 4 of 154 cases of disseminated lupus erythematosus the condition occurred in pregnancy or shortly after delivery. Crawford [10] cited the cases of three patients with lupus erythematosus during pregnancy. In one patient the disease, of one year's duration, became worse during pregnancy but improved one month after delivery. The other two patients had the chronic discoid type which became more acute during pregnancy. In one the mother died and the infant survived, and in the other the mother survived and the child died.

6. Montgomery, H.: Disseminated Lupus Erythematosus as a Systemic Disease, Oxford Medicine, Vol. 4 (Pt. 1) Chap. 16, p. 44 (41), 1950.

7. Baehr, G., and Pollack, A. D.: Disseminated Lupus Erythematosus and Diffuse Scleroderma, J. A. M. A. **134**:1169-1174 (Aug. 2) 1947.

8. Fromer, J. L.: The Use of Testosterone in Chronic Lupus Erythematosus: Preliminary Report, Lahey Clin. Bull. **7**:13, 1950.

9. Michelson, H. E.: The Problem of Lupus Erythematosus, California Med. **70**:1, 1949.

10. Crawford, G. M., and Leeper, R. W.: Diseases of the Skin in Pregnancy, Arch. Dermat. & Syph. **61**:753 (May) 1950.

QUESTIONNAIRE

We present here some of the answers to the questionnaire. Montgomery wrote that in acute disseminate lupus erythematosus, the onset of the lupus erythematosus was preceded by normal pregnancy in one patient, and the patient died 60 days after delivery and 39 days after the onset of acute disseminate lupus erythematosus. One patient with acute disseminate lupus erythematosus had toxemia of pregnancy, one patient a kidney infection, and one patient a salpingitis. It is doubtful whether one of these patients is still alive, as he has lost track of her. The other two are recent patients.

In a group of patients with subacute disseminate lupus erythematosus, Montgomery stated, one had two miscarriages at seven and three months, respectively, with flare-up of the lupus erythematosus after each; one had difficulty at delivery after an earlier and unsuccessful attempt at abortion; one had two pregnancies without trouble; in one disseminated followed discoid lupus erythematosus 25 years after menopause; one patient had a salpingo-oophorectomy 12 years before the onset of disseminate lupus erythematosus; in one patient disseminate lupus erythematosus developed immediately after panhysterectomy, and one patient had a flare-up of the lupus erythematosus after therapeutic castration.

In a group of patients with chronic disseminate lupus erythematosus, Montgomery reported one patient who had a normal pregnancy without flare-up but in whom the disease flared after delivery; one patient who had a normal pregnancy with improvement in the lupus erythematosus, and one patient who had a hysterectomy without flare-up of the lupus erythematosus. There were nine cases of subacute disseminate lupus erythematosus after the age of 45 in women and two in men. One woman had died. There were four cases in which chronic disseminate lupus erythematosus developed after 45 in women and one in a man. All are alive.

Goldberg reported the cases of two patients with acute lupus erythematosus who survived their illness, and one 18 months later gave birth to twins, one of whom died. The second patient became pregnant two years after the onset of her illness, but aborted in the fourth month. The question was raised by Goldberg as to whether fetal deaths or abortion tendencies are increased in acute lupus erythematosus.

Rothman cited the case of a patient with subacute lupus erythematosus which recurred each time during the first trimester of three successive pregnancies, and in the first pregnancy the eruption cleared as soon as spontaneous abortion occurred. The second pregnancy was terminated, and the lesions receded again. In the third pregnancy a severer attack developed and therapeutic abortion was performed, with rapid improvement of the lesions. Guy described a patient with subacute lupus erythematosus which had lasted for several years but cleared during several pregnancies and recurred after each pregnancy.

HORMONAL CHANGES IN PREGNANCY

Hormonal changes in pregnancy and in the menstrual cycle should be considered. In the first half of the menstrual cycle the estrogenic hormone is secreted under the influence of the follicle-stimulating hormone of the anterior pituitary which causes increased endometrial growth. The Graafian follicle develops during this period, and ovulation takes place about 14 days before menstruation begins. At about the seventh day of the cycle, progesterone is secreted, also because of estrogenic hormone

gonadotropic stimulation by the anterior pituitary, and this leads to secretory changes in the endometrium. If fertilization of an ovum occurs, the corpus luteum remains active and increases its production of progesterone, which inhibits mobility of the uterus. Estrogen and progesterone are present throughout the pregnancy, and the hormone concentration changes slowly. The amount of chorionic gonadotropin is present in increasing concentration as pregnancy continues and does not disappear until shortly after delivery. Progesterone increases slowly until just before labor and then disappears. We have been unable to tie these hormonal changes with development or aggravation of lupus erythematosus.

KETOSTEROIDS IN PREGNANCY

According to Dobriner and his associates,[11] 19 ketosteroids have been isolated in pregnant women. The following 11 are found only in urine of pregnant women: 135-136°, allopregnanedione, pregnanedione, 117-121°, 120-125°, 235-237°, allopregnanediol-3-α-6-one-20, 192-194° $C_{21}H_{34}O_3$, Δ^2 allopregnane-3β-one-20, 272-275°, 209-210°, $C_{21}H_{34}O_3$. They also stated that three other ketosteroids, 3-Δ^3-andro-

Results of Questionnaires on Lupus Erythematosus with Pregnancy *

	Lupus Erythematosus		
	Acute	Subacute	Chronic Discoid
Patients, no.	56	13	31
Improved	17	7	15
During pregnancy	5	..	..
After pregnancy	12	..	..
Became worse	25	3	3
Maternal deaths	14	6	0
No change	14	3	13
Fetal deaths	10	..	..
Neonatal deaths	6	..	..
Spontaneous abortions	..	6	1

* Number of questionnaires sent, 280; returned, 120; tabulated, 100.

stenone-17, Δ^3_5-5-androstadienone, and etiocholanol-3(α)-one-17, are found in urine of pregnant and nonpregnant women. In addition five steroids were isolated which were already previously isolated in pregnant women's urine by other investigations. These were isoandrosterone, androsterone, pregnanol-3(α)-one-20, allopregnanol-3(α)-one-20, and allopregnanol-3(β)-one-20. Five of the most abundant steroids, three of which are normally present in all subjects and two of which appear in significant amounts only in gravid females, were studied in detail by contrasts between normal and pregnant women.

Pregnanolone and allopregnanolone are excreted in considerable amounts during pregnancy; they occur only occasionally in the urine of nonpregnant women. Allopregnanolone seems to be excreted at a relatively constant level of 1 to 2 mg. per 24 hours throughout pregnancy, whereas pregnanolone increases steadily from 3 mg. per 24 hours during the third month to a value exceeding 40 mg. per 24 hours at the ninth month. Pregnanolone parallels the excretion of the pregnanediol complex. Following delivery, steroid excretion promptly returns to the amount and pattern characteristic of normal women.

11. Dobriner, K.; Lieberman, S.; Rhoads, C. P., and Taylor, H. C., Jr.: Urinary Excretion of Ketosteroids in Pregnancy, Obst. & Gynec. Surv. **3**:677-679, 1948.

Androsterone and its isomer etiocholanolone, major constituents of the urine of normal women, are excreted in nearly normal amounts during early pregnancy. By the eighth month, androsterone has disappeared from urine, and etiocholanolone is much reduced. Both reappear after delivery. In pregnancy, urinary steroid production is altered.

Two metabolites of adrenal cortex origin, present in normal women, are 11-keto-etiocholanolone and 11-hydroxy-androsterone. The former is excreted in normal amount through pregnancy, but the latter is absent in pregnancy. This again points to alteration in production of adrenocortical precursors, which is part of growth requirements.

REPORT OF CASES

CASE 1.—A white woman, aged 21, had a normal full-term pregnancy. Two weeks before delivery a high fever, pains and swelling of the joints, and an erythematous patchy macular eruption on the face and neck were noted. When the patient was admitted, her temperature was 101 F., the blood pressure was 110 mm. of mercury systolic and 70 mm. of mercury diastolic, and the pulse rate was 120. The findings from examination of the blood were as follows: hemoglobin, 51%; red cell count, 2,400,000, and white cell count, 1,800, with 78% lymphocytes, 6% eosinophiles, and 16% polymorphonuclear leucocytes. The sedimentation rate was increased. The ratio of albumin to globulin was 0.6, and the urine contained albumin (3+). She became very toxic, with a temperature ranging between 104 and 106 F. for a period of three weeks. Blood cultures were positive for a hemolytic Micrococcus (Staphylococcus). In spite of massive doses of penicillin and blood transfusions, five weeks after onset of the illness she died. Sections of skin showed the pathologic picture [12] of acute disseminated lupus erythematosus. Consent for autopsy was not obtained. The child died two weeks after delivery.

CASE 2.—A white woman, aged 25, in her sixth month of second pregnancy manifested fever, malaise, weakness, and an erythematous eruption on the bridge of the nose. She had a temperature of 101 to 103 F.; the average pulse rate was 110, and the blood pressure was 96 mm. of mercury systolic and 50 mm. of mercury diastolic. Results of laboratory examination of the blood were as follows: hemoglobin, 75%; red cell count, 4,120,000, and white cell count, 5,700, with a normal differential count. The albumin: globulin rate was 1.4: 1.0, and the urine showed a trace of albumin. She became toxic, and swelling of the joints developed, with stiffness. Pregnancy was interrupted and oophorectomy performed, but she died eight weeks after onset of illness and three weeks after interruption of pregnancy. The clinical diagnosis was acute lupus erythematosus.

CASE 3.—R. R., a Chinese woman, aged 21, was first seen Nov. 3, 1949. She had one 3-year-old child, living and well. A second pregnancy had resulted in a stillbirth in May, 1948. In April, 1949, an eruption appeared on the face, but we were unable to obtain any definite data concerning this eruption. It rapidly became more generalized, and on Nov. 2, 1949, the patient was delivered of a premature baby who died soon after birth of gangrenous pneumonia. For the past four months the patient had a generalized, livid, erythematous, scaly, and, recently in some areas, crusted dermatitis. Her urine showed albumin (3+), with many pus cells which may have been due to a cystitis. She had a high fever, and examination of the blood showed hemoglobin of 50%, a red cell count of about 3,000,000, and an average white cell count of 10,000. The reading of the thymol turbidity test was 25.6, and the cephalin-cholesterol flocculation was 3+ in 24 and 48 hours. At the time of the first examination, the patient's eruption was diagnosed as an acute disseminated lupus erythematosus. On Nov. 9, 1949, the patient was removed to another hospital in hopes of obtaining corticotropin (ACTH) or cortisone, but within 24 hours she had a temperature of 108 F. and died.

12. Bundick, W. R., and Ellis, F. A.: Lupus Erythematosus: Classification, Diagnostic and Prognostic Value of Biopsies, South. M. J. **44**:204, 1951.

RESULTS OF CASES AND QUESTIONNAIRE

Two of our patients and their newborn children died soon after delivery, and another woman died several weeks after the interruption of her pregnancy in the sixth month.

The results of the questionnaire are shown in the accompanying table. Apparently acute lupus erythematosus frequently has had a disastrous effect (about 30%) on the fetus, or newborn child. In the acute type, in approximately 45% the disease became worse or the mothers died during pregnancy. In 14 patients pregnancy had no effect on the acute lupus erythematosus; 5 patients improved before and 12 improved after delivery. The total number of patients who were reported as improved or unaffected by their pregnancy was 31 (55%).

The subacute type of lupus erythematosus with pregnancy showed no constant effect on the mothers. Some improved, others remained stationary, and others became worse, but the changes were about what one would expect in subacute lupus erythematosus without pregnancy. In the subacute form there were six (46%) spontaneous abortions, which suggests that even subacute lupus erythematosus may have a serious effect on the fetus. Since there were only 13 patients in this group, the conclusion drawn may be questionable.

Chronic discoid lupus erythematosus associated with pregnancy had practically no effect on the mother or the pregnancy.

COMMENT

Should a patient with lupus erythematosus be advised against becoming pregnant? We think that, if the lupus erythematosus is chronic or subacute, the mother, more than likely, will go through the pregnancy uneventfully, although in the subacute form the prognosis for the fetus is relatively poor.

In the acute type of lupus erythematosus, because it is such a serious disease, it is doubtful that the risk for the mother and/or the child is advisable, even though figures do not prove that the prognosis is made worse by pregnancy. Only 14 of the 56 patients died, and in 11 other patients the lupus erythematosus became worse. These figures are about the same as one might expect in 56 patients with acute lupus erythematosus without the complication of a pregnancy, in the time covered by the pregnancy. However, the 30% fetal or neonatal mortality must also be considered.

Because of previous literature concerning the effect of castration and menopause on lupus erythematosus, this circumstance was also included in the questionnaire. We found that acute, subacute, and chronic discoid lupus erythematosus may occur after the menopause. In answers to the questionnaire, lupus erythematosus first appearing after the menopause was reported as follows: acute, 37 cases; subacute, 39 cases, and chronic discoid lupus erythematosus, 61 cases. The menopause was found to have no consistent effect upon the lupus erythematosus.

This report was based on a questionnaire because apparently no one dermatologist or obstetrician has seen enough patients with lupus erythematosus associated with pregnancy to make a report which would show the prognosis.

CONCLUSIONS

1. When accompanied by acute disseminated lupus erythematosus pregnancy may result in 30% fetal mortality.

2. In acute lupus erythematosus the maternal mortality rate (25%) does not seem to be unduly influenced by pregnancy.

3. In pregnancy accompanied by subacute disseminated lupus erythematosus there was 46% fetal mortality, but pregnancy, with a few exceptions, had little or no effect on the course of the disease in the mother.

4. In pregnancy accompanied by chronic discoid lupus erythematosus no consistent effects on the mother or the child were noted.

5. Acute, subacute, or chronic types of lupus erythematosus, may have their onset after the menopause, but the prognosis is apparently not altered by the endocrine changes accompanying menopause.

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CORTISONE ACETATE IN SKIN DISEASE

Local Effect in the Skin from Topical Application and Local Injection

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CINCINNATI

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CORTISONE acetate (cortone®) has been found to have a local effect in various diseases of the eye, especially those of an inflammatory or exudative nature.[1] In ophthalmology, suspensions of cortisone have been used locally as drops and by subconjunctival injection and ointment. In some instances it was necessary to dilute the suspension 1:4 because of local irritation. Special ophthalmic preparations of cortisone with buffered solutions are available. However, topical application does not have any effect on exudation in the vitreous body according to Woods.[2] After injection into the anterior chamber Woods [1h] has reported a heavy flocculent mass disappearing within 24 to 48 hours. After subconjunctival injection remnants can be seen for several weeks. The advantages of local cortisone therapy are

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Hypospray® jet injection instruments were furnished by J. M. McKibbin, R. P. Scherer Corporation, Detroit.

Cortisone acetate (cortone®), water-soluble ester of cortisone, and compound F (17-hydroxycorticosterone acetate) were furnished by Dr. J. M. Carlisle, Merck & Company, Inc., Rahway, N. J.

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1. (*a*) Steffensen, E. H.; Olson, J. A.; Margulis, R. R.; Smith, R. W., and Whitney, E. L.: The Experimental Use of Cortisone in Inflammatory Eye Disease, Am. J. Ophth. **33**:1033 (July) 1950. (*b*) Henderson, J. W.: Clinical Observations of the Use of Cortisone in Ophthalmic Diseases, Proc. Staff Meet., Mayo Clin. **25**:459 (Aug. 2) 1950. (*c*) Woods, A. C.: Clinical and Experimental Observation on the use of ACTH and Cortisone in Ocular Inflammatory Disease, Am. J. Ophth. **33**:1325 (Sept.) 1950. (*d*) Jones, I. S., and Meyer, K., cited by Woods.[1c] (*e*) Woods, A. C., and Wood, R. M.: The Action of ACTH and Cortisone on Experimental Ocular Inflammation, Bull. Johns Hopkins Hosp. **87**:482 (Nov.) 1950. (*f*) Rome, S.; Koff, R.; Kasper, R.; Button, R.; Commons, R., and Starr, P.: ACTH and Cortisone in Ocular Inflammation, Parenteral and Local Use, Ann. West. Med. & Surg. **4**:799 (Dec.) 1950. (*g*) Harvey, A. M.; Howard, J. E., and Kattus, A. A.: The Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone on Certain Diseases of the Eye in Which Hypersensitivity Plays a Role, Bull. Johns Hopkins Hosp. **87**:461 (Nov.) 1950. (*h*) Woods, A. C.: Personal communications to the authors.

2. Woods.[1c] Woods and Wood.[1e]

obvious. These include the utilization of smaller quantities of medication, avoidance of systemic side-effects, therapy of ambulatory patients, and therapy of aged or debilitated patients. In one case Reeder and Mackey [3] administered nebulized cortisone, and later aureomycin, to a patient with bacterial pneumonia. Pellets of cortisone are said to have been implanted in the skin, but these are used primarily for their systemic effect. Local hyperpigmentation has been observed to develop about the implanted pellet.[4]

The studies of Taubenhaus and his associates [5] are of interest. With the addition of cortisone to turpentine, they have been able to show changes in the reaction induced by turpentine injected subcutaneously in animals. The fibroblastic and inflammatory response was influenced with the addition of cortisone to turpentine.

Baker and Castor [6] have studied the effects of cortisone in alcohol when applied to the skin of male rats. After daily applications for 80 or more days there were cessation of hair growth, thinning of the epidermis, reduction in the size of epidermal cells and sebaceous glands, atrophy of collagen fibers, and reduction of cellularity of the connective tissue. No change was noted in the elastic fibers. If the applications were continued for 180 days, there was refractoriness of the hairs to further change.

In a small series of patients, Spies and Stone [7] used an ointment containing 5 mg. of cortisone to the gram. Encouraging results were reported. Hailey [8a] has recently reported the ineffectiveness of cortisone ointment (2.5 to 3.5 mg. per gram) in patients with eczematoid dermatitis. Newman and Feldman [8b] reported good results in prolonged topical therapy with cortisone in discoid lupus erythematosus and necrobiosis lipoidica diabeticorum.

Since cortisone is supposed to inhibit cellular reaction at the mesenchymal level, it appears quite proper to attempt to study its supposedly purely local action. The exact mechanism or mechanisms are not known. Suggested modes of action have included a vascular protective component which may increase the resistance of the wall of the capillary or small vessel, a diminution of hyaluronidase activity, or an inhibition of fibroplasia. It is essential to emphasize that the basic underlying condition is unaffected by the hormonal therapy.

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3. Reeder, W. H., and Mackey, G. S.: Nebulized Cortisone in Bacterial Pneumonia, Dis. Chest. **18**:528 (Dec.) 1950.

4. Hertz, R.: Personal communications to the authors.

5. Taubenhaus, M., and Amromin, G. D.: The Effects of the Hypophysis, Thyroid, Sex Steroids and the Adrenal Cortex upon Granulation Tissue, J. Lab. & Clin. Med. **36**:7 (July) 1950.

6. Baker, B. L., and Castor, C. W.: Cutaneous Atrophy Induced by Local Treatment with Adrenocortical Steroids, Anat. Rec. **106**:173 (Feb.) 1950. Castor, C. W., and Baker, B. L.: The Local Action of Adrenocortical Steroids on Epidermis and Connective Tissue of the Skin, Endocrinology **47**:234 (Oct.) 1950.

7. Spies, T. D., and Stone, R. E.: The Effect of Local Application of Synthetic Cortisone Acetate on the Lesions of Iritis and Uveitis of Allergic Dermatitis, and of Psoriasis, South. M. J. **43**:871 (Oct.) 1950.

8. (*a*) Hailey, H.: The Ineffectiveness of Cortisone Applied Locally in Eczema, Schoch Letter, April, 1951. (*b*) Newman, B. A., and Feldman, F.: Effects of Topical Cortisone on Chronic Discoid Lupus Erythematosus and Necrobiosis Lipoidica Diabeticorum, J. Invest. Dermat. **17**:3 (July) 1951.

OUTLINE OF STUDY

In the attempt to set up a critical study of the local action of cortisone on the skin, the first consideration appears to be the use of suitable controls. For the employment of a steroid substance such as cortisone, the control suggested by many was cholesterol. For the injection techniques it appeared necessary, as several have suggested, that instead of the plate-type crystals of cholesterol an acicular type be used. These are similar in shape and configuration to the crystals of cortisone. As yet, we have been unable to obtain the acicular type of cholesterol. The vehicle must be used as a control since it is certainly not a completely inert substance. This vehicle is as follows: 1.5% benzyl alcohol, 0.9% sodium chloride, 0.4% sorethytan (20) monooleate, 0.5% sodium carboxymethylcellulose, and distilled water.

Experiments have recently been initiated with a water-soluble ester of cortisone.

The majority of local injections were given by hypospray® jet injection apparatus,[9] volumes of 0.6 to 1.0 cc. per dose being used. In a small series of patients, intradermal injections by the syringe and needle were given. The cortisone-free suspension was also used in this small series. Cortisone "suspension" in saline, free of vehicle, was also used chiefly to study crystal deposits in the skin. Schneebeli, Lowe, and Dougherty,[10] have reported inflammatory reactions in tissue from the use of the suspending agent. It is the opinion of Dougherty and his associates [10b] that the sodium carboxymethylcellulose is chiefly responsible for the azurophilic fibroblastic inclusions. Sorethytan (20) monooleate ("tween 80") was also weakly effective in producing these inclusions. After the injection of 1 mg. of cortisone suspension in animal skin these inclusions appear within four hours, and the maximum reaction is at 24 hours, when the number of cells affected is 40%.

For the studies with the topical application of cortisone, the controls included the ointment base alone as well as cholesterol in the ointment base.

The following materials were employed in the study:

1. Cortisone ointments—concentrations from 125 to 750 mg. per 30 gm. of ointment base. The ointment bases were aquaphor® (an oxycholesterol-petrolatum ointment base), "vanibase" (cetyl and stearyl alcohol, sodium lauryl sulfate, white wax, and propylene glycol), "mul-sol" (spermaceti, wax, liquid petrolatum, and cetyl alcohol), mixtures of aquaphor® and "mul-sol," polyethylene glycol (carbowax®) 1500 and zinc stearate.

2. Cholesterol ointment—150 to 500 mg. per ounce (30 gm.) base in the same vehicles as 1 above with the exception of carbowax® 1500 and zinc stearate.

3. Ointment bases with saline.

4. Cortisone suspension by hypospray® jet injection instrument, approximately 25 mg. per dose.

5. Cortisone-free suspension by hypospray® jet injection instrument, approximately 1.0 cc.

6. Cholesterol in same suspension material by hypospray® jet injection instrument apparatus, approximately 25 mg.

7. Cortisone suspension, intradermally, 0.2 cc.

8. Cortisone, water-soluble ester, intradermally, 0.2 cc.

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9. Larrick, L. E., and Thompson, R. G.: The Hypospray and Its Relationship to Dermatology, J. Invest. Dermat. **13**:361 (Dec.) 1949. Preston, R. H.; Goldman, L., and Thompson, R. G.: The Use of the Hypospray in Dermatology, A. M. A. Arch. Dermat. & Syph. **64**:327 (Sept.) 1951.

10. (*a*) Schneebeli, S.; Lowe, S., and Dougherty, T. F.: Azurophilic Inclusions in Connective Tissue Cells, abstracted, Am. A. Anat., 1950. (*b*) Dougherty, T. F.: Personal communication to the authors.

9. Cortisone, water-soluble ester, with hypospray® instrument, approximately 1.0 cc. (14 mg.).

10. Compound F (17-hydroxycorticosterone acetate) suspension, intradermally, 0.2 cc., and ointments, 2.5% and 5.0%.

Selected patients with a variety of dermatoses were secured. Special form outlines were kept on these patients. Detailed and critical animal investigative studies in the department of dermatology are being done at Kettering Laboratory by Nilzén.[11] It is hoped that these studies and similar studies of Nilzén with other hormones will serve to control our clinical studies in a more critical fashion. An effort was made in some instances to provide the physician himself with coded materials so that even he did not know whether he was using cortisone or an inert control.

TOPICAL APPLICATION OF OINTMENTS

The ointments were given to the patients in ½- or 1-oz. jars (15 or 30 cc.). The patients were instructed to rub a small amount of the ointment vigorously on the skin three to six times daily. Controls were substituted, often without the patient's knowledge, or applied to similar lesions at other sites concomitantly. In every case of reported improvement, controls were employed. One hundred and two patients were included in this group. There was no single case of irritation or sensitization attributed to the cortisone suspension or its suspending material. In concentrations varying from 125 to 750 mg. of cortisone per 30 gm. of base, in bases known to penetrate the skin, there were a few patients in whom the ointment was reported to be of some direct value. In these patients the condition, for the most part, was not chronic in nature, and the results could not always be controlled, for the condition would clear spontaneously of its own accord, as, for example, in contact dermatitis. Opportunity was offered, for example, in the contact-dermatitis group to treat nine additional patients with poison ivy dermatitis within 12 hours after the appearance of the initial group of blisters. In none of these patients did the cortisone ointment prevent local spread of lesions. In a control series given cortisone orally the response in early cases was often dramatic. In other cases of reported improvement, the period of observation was not of sufficient length. In a patient with hypersensitivity to nickel, proved by a positive reaction to a patch test, 2% nickel sulfate solution was mixed with the cortisone suspension, and simultaneous controls were done with the nickel sulfate solution alone and also with a five-cent coin. The reactions to all three contact tests were positive. In another patient with proved eczematous hypersensitivity to nickel, local injections of cortisone as mentioned below did not influence the manifestation of the positive reaction to a patch test with nickel in the injected area. In contact dermatitis of the eyelids the effect of the cortisone ointment appeared better than in the controls. The investigative studies with the pigmented nevi and the patient with Addison's disease were included because of previous studies[12] with corticotropin (ACTH) and cortisone in the development of new junctional nevi.

In this series, then, with the materials available, and in the concentrations employed, ointments containing cortisone were not effective, whereas in many of

11. Nilzén, Å.: Personal communication to the authors.

12. Goldman, L., and Richfield, D.: The Effect of Corticotropin and Cortisone on the Development and Progress of Junctional Nevi, J. A. M. A. **147**:941 (Nov. 3) 1951.

these conditions systemic therapy with cortisone is effective. If there is local action of cortisone acetate in the skin, then such variable factors as incomplete absorption,

TABLE 1.—*Effect of Cortisone Suspension in Ointments Applied to the Skin*

Disease	Patients, No.	Mg. Cortisone/Gm. Vehicle	Average Duration of Therapy, Wk.	Results	Controls, No.	Controls, (Results)	Remarks
Psoriasis	19	5/16.6	3	Improved, 5; no results, 13; flare, 1	5	Improved, 3; no results, 2; flare, 0	Of the 18 patients in series responding to cortisone systemically, 3 did not respond to cortisone locally
Atopic dermatitis	8	5/16.6	2	Improved, 4; no results, 3; flare, 1	6	Improved, 3; no results, 3	.....
Eczematous and "eczematoid" dermatitis group	44	4.1/25.0	2-3	Improved, 20; no results, 18; flare, 6	18	Improved, 8; no results, 6; flare, 4	Difficult to evaluate results since some were cleared before any controls could be tried
Solar dermatitis	3	10/25	2	Improved, 3; no results, 0; flare, 0	No controls used	.....	.....
Lupus erythematosus group							
Subacute	7	5/25.0	2	Improved, 3 (subacute); no results, 3; no results, 2	..	.....	One patient given cortisone systemically; ointment used on persistent lesion had no effect
Discoid	2	5/10	4				
Scleroderma (only one area treated)	4	5/10	4	Improved, 0; no results, 4	0	.....	One area became hyperpigmented
Dermatitis herpetiformis (local area)	2	5/10	6	Improved, 0; no results, 2	0	.....	When topical applications used all over body, then some improvement (systemic?)
Pigmented nevi	4	10	1 mo.	Improved (?), 1; no results, 3; flare, 0	0	.....	Patient reported one blue nevus faded; did not return, so report could not be checked
Addison's disease (local control area)	1	10	3	Flare, 1 (hyperpigmentation)	1	No change	Even though patient was on systemic therapy, local application of cortison increased pigment
Keloids	5	5/10	3-4	Improved, 1; no results, 4	1	No change	.....
Miscellaneous group							
Eczema mammarium symmetricum	1						
Epidermolysis bullosa	3	10/25					
Rosacea	2						
Milia	1						
Fox-Fordyce disease	1						
Lichen urticatus	1			No results on prolonged therapy save for questionable results in rosacea.			
Xanthoma tuberosum	2						
Urticaria pigmentosa	1						
Insect bite	2						
Prevention of nickel patch test reaction	1	(was not effective in "prevention")					
Postadhesive leucoderma	1						

lack of penetrability, and diffusion of cortisone from the base are suggested to explain our failures. It is necessary to add that all our patients treated in the final phase of this study had used ointments containing 10 to 25 mg. per gram of ointment base.

LOCAL INJECTION OF CORTISONE

There is very little pain associated with local injection of the cortisone suspension. In fact, several biopsy specimens were removed from the skin without additional procaine. In most instances there were no reactions to the local injections with either the hypospray® jet injection instrument or the syringe and needle. Bleeding was occasionally noted, especially with superficial injections with the hypospray.® In one patient a hematoma developed in a superficial patch of psoriasis. No hemorrhages were produced, however, with later injections with this instrument. A grossly nodular reaction developed in both the hypospray® and the small syringe and needle series. This reaction would reach its maximum in approximately 24 hours, was observed as early as two hours after injection, and in some instances persisted as long as three weeks. The frequency of this nodular infiltration after the injection of cortisone in suspension in this series was approximately 10%. One patient with a severe eczematoid dermatitis of the hand and forearm had 1.0 cc. cortisone suspension injected with the hypospray® into an active area of the forearm. An extensive brawny induration of that area developed. This subsided after several weeks. Repeated injections of cortisone in other areas of similar intensity on the other forearm did not result in any nodular type of reaction. The series of superficial injections into the skin by the hypospray® jet injection instrument included 65 patients with a total of 135 injections, that of superficial injections in the skin by syringe and needle, only 14 patients. A number of patients in these series had prior or subsequent systemic cortisone therapy.

The following preliminary detailed biopsy studies have been done:

Normal Skin

Cortisone suspensions—injected by needle and hypospray,® both a single injection and also two superficial injections with the hypospray® of 1.0 cc. cortisone in the same area in some biopsies

5 minutes
2 hours
24 hours
48 hours

Suspending material without cortisone—injection by needle and hypospray®

24 hours
48 hours

Cortisone without vehicle

5 minutes
24 hours

Cholesterol suspensions—injection by needle and hypospray®

24 hours
48 hours

Cortisone water-soluble ester—injection by needle and hypospray®

24 hours
48 hours

Discoid lupus erythematosus

72 hours after hypospray® injection

Dermatitis medicamentosa

48 hours after 0.2 cc. intradermal injection by needle
4 hours after superficial hypospray® injection

Detailed biopsy studies are now under way with compound F in normal skin, eczematous skin in mosquito bite, Frei test, and tuberculin reactions. The biopsy sections were stained by hematoxylin and eosin, and trichrome stains, and by Suskind [13] at Kettering Laboratory with Sudan black, Sudan IV, digitonin, and the Liebermann-Burchardt test. All sections were examined under ordinary bright-field microscope, dark-field microscope, polarizing microscope, and by phase contrast with the Galileo microscope. In addition, frozen sections after formaldehyde fixation were examined.

Even with the detailed examination of the skin, five minutes after injection, it was not possible, with the techniques enumerated, in fixed tissues to detect crystals of cortisone in the skin. Recently Nilzén has demonstrated crystals of cortisone in frozen sections of unfixed animal skin after injection. In studies of one of us (L. G.) with O'Hara, crystals of cortisone and compound F, have been identified in human skin. The tissue reactions to cortisone suspension began with a slight perivascular reaction in the immediate area of injection. Later the infiltrate spread extensively in the skin, first superficially and then in the mid portions of the dermis. In the trichrome stains these masses were slightly eosinophilic. These were homogenous and later became coarse granular and invaded by polymorphonuclear leucocytes and lymphocytes and many histiocytes. These masses were found deeply, in some instances in the panniculus, even with "intradermal" injections of only 0.2 cc. with the needle and syringe. The inflammatory infiltrate included lymphocytes, histiocytes, eosinophiles, including bizarre types, and many pyknotic cells. Special efforts were made to study the puncture areas of the epidermis made by the superficial injections with the needle and the hypospray® instrument. These traumatic areas appeared unusually prominent, more so even than one would expect from superficial injections of crystalline suspensions. The tissue distortions in the dermis were no more marked than usual with such a superficial injection by the hypospray.® It was surprising to see extensive deep tissue involvement in the specimen when the skin appeared normal to inspection and palpation. With the use of the suspending-agent mixture alone, a similar reaction developed. The reactions to the water-soluble ester of cortisone were less intense in the few sections studied. However, the same type of basophilic masses were found in the dermis. The details of these tissue reactions together with those of compound F will be reported later by Goldman and O'Hara.[13a]

These reactions demonstrate that there is some severe tissue reaction to the suspending agent, as previous investigators have found. No tissue extractions or spectrophotometric analyses were done. To produce these tissue reactions, there may be a direct mechanical irritation, even with the syringe and needle spray, from the crystals which, at least initially, may be insoluble. A suitable form of needle type of cholesterol crystals would be necessary here to prove this concept of mechanical crystal irritation. Even with the presence of cortisone, the inflammatory reaction is striking, extensive, and persistent. There is a definite suspicion that such concentrations of cortisone as were injected may be toxic, at least locally.

13. Suskind, R. R.: Personal communications to the authors.

13a. Goldman, L., and O'Hara, E. H.: The Local Tissue Reactions to Cortisone and Compound F: I. The Detection of Crystals Following Local Injection, to be published.

TABLE 2.—*Effect of Local Superficial Injections of Cortisone Suspension into the Skin by Hypospray® Jet Injection Instrument*

Disease	Patients, No.	Injections,* No.	Reactions	Results	Controls, No.	Controls, Results	Remarks
Normal skin	5	8	Nodule, 1	..	..	..	.....
Discoid lupus erythematosus	3	1-56	0	Improved, 1; no results, 2; flare, 0	0	..	Improvement not remarkable save for patient who received 900 mg. over 12-wk. period; degree of involution not marked
Subacute lupus erythematosus	3	5	Nodule, 2; bleeding mild, 1	Improved, 0; no results, 3; flare, 0	..	..	In 1 patient a transient improvement noted
Psoriasis (local lesion)	10	2	Nodules, 2; hematoma, 1	Improved, 0; flare, 0; no results, 10	2 (procaine)	0	One patient had improved on cortisone systemically
Dermatitis herpetiformis	4	6	Bulla, 1	Improved, 0; no results, 4; flare, 0	..	..	In 1 patient a blister still spreading after injection of 25 mg. cortisone into edge of skin adjacent to blister
Atopic dermatitis (local area)	3	3	0	Improved, 1; no results, 1; flared, 0	0	..	Adjacent area flared in 1 patient
Secondary localized neurodermatitis	6	9	0	Improved, 0; no results, 6; flare, 0	4 (procaine)	..	Control improved
Eczematoid dermatitis group	5	8	Extensive brawny induration	Improved, 2; no results, 3; flare, 0	1	0	In 4 cortisone given directly into the area; reaction in only 1
Drug eruption	3	3	0	Improved, 0; no results, 3; flare, 0	..	..	No localized effect in extensive drug rash
To prevent development of positive patch test reaction	2	2	0	0	..	..	Did not prevent the development of a positive patch test reaction
Insect bites	3	3	0	..	1	0	No prevention of reaction to insect bites (pediculus and mosquito); as therapy, one cleared more rapidly than control
Erythema perstans (?)	4	5	0	Improved, 1; no results, 3; flare, 0	2 procaine 1 pen.	0 0	.....
Panniculitis (local lesions)	3	3	0	Improved, 3; no results, 0; flare, 0	0	..	No controls
Lichen planus (local lesions)	2	2	0	Improved, 0; no results, 2; flare, 0	..	..	.....
Subepidermal nodular fibrosis (single early lesions)	2	7	0	Improved, 2; no results, 0; flare, 0	..	..	Controls necessary for this group; edema in 1 patient but no nodule; period of observation too short
Scleroderma†	1	24	0	Improved, 0	..	..	Some softening of tissue, no biopsy
Mycosis fungoides	2	8	0	Improved, 0; no results, 2; flare, 0	..	.	.....
Leukemic nodule skin	1	1	0	Improved, 1	..	..	Lesion showed definite improvement; temporary; no control
Solitary nodular urticaria pigmentosa	1	1	Bleeding mild, nodule, 1	Improved, 1	..	..	Mother reported no (?) whealing on rubbing and decrease in size of lesion; no control
Xanthoma tuberosum multiplex	1	3	Bleeding mild	Improved, 1	Control (procaine)	..	Control area improved also (?)
Junctional nevus	1	1	Nodule, 1	..	..	..	No excision done yet; nevus had appeared under cortisone therapy for lupus erythmatosus; cortisone still used as maintenance therapy; some pigmentation about area of injection adjacent to nevus

* Approximately 25 mg. per injection.
† Area used 3 in. (7.6 cm.) in diameter.

There is, then, irritation both from the cortisone and from the suspending material. The study of the tissue reaction is described in detail, for this may explain some of the lack of local therapeutic response in this series. We have no exact data on the frequency of the nodular reaction in the buttock to the intramuscular injections of cortisone suspension, but it is our impression from our series that this is an uncommon reaction here. Forsham [14] indicates that the percentage in his series may be 1 to 2%. It is hoped that the work of Nilzén [11] and others, and perhaps the use of other mixtures of cortisone, will clear up the confusion of the mechanism of the local inflammatory reaction of cortisone suspension in the skin.

Examination of Table 2 shows that there was apparent improvement in a few conditions, such as nodular leukemia cutis, panniculitis, subepidermal nodular fibrosis, and perhaps xanthoma tuberosum multiplex. The results in the small

TABLE 3.—*Effect of Cortisone Suspension Injected Intradermally*

Patient	Disease	Dosage, Cc.	Reaction	Results
1, R.	Insect bites following local injection of cortisone	1.0	Nodule	No effect on intensity of insect bite reaction
2, R.	As control area	1.0	Nodule	.....
3, J. R.	As control, cortisone 0.1 plus saline 0.1 cc.	0.02	None	.....
4, J. R.	Cortisone plus insect extract	0.02	None	Intensity of reaction same as with extract with 25% saline
5, H.	Thephorin® dermatitis	1.0	Nodule	No prevention of positive patch test
6, T.	Dermatitis medicamentosa (chloral hydrate)	0.2	Nodule	No local blanching effect on drug rash
7, P.	Nickel dermatitis	1.0	Nodule	No prevention of positive patch reaction
8, F.	Discoid lupus erythematosus	0.5	None	No effect
9, A.	Discoid lupus erythematosus	0.2	None	No effect
10, P.	Normal skin	0.2	Nodule	.....
11, G.	Normal skin	0.2	None (5 min.)	.....
12, R.	Normal skin	0.2 (water soluble ester), 2 times	None Slight infiltration	.....
13, W.	Dermatitis herpetiformis	0.5	None	No effect on bulla
14, F.	Atopic dermatitis	0.5, 4 times	Some infiltration	Some transient relief of pruritus

group with lupus erythematosus were, unfortunately, not striking. Furthermore, of all of these improved conditions, only in the case of xanthoma tuberosum multiplex was any control injection used, and here the control was only 2% procaine. A series of early keloids has just been studied with both the needle and the hypospray.® Yet, these results with local injection of cortisone were significant enough to warrant further consideration of this type of therapy with this and related compounds and use of good controls. In light of our recent experiments with compound F it appears that studies with the local injection of this steroid into tumors of the lymphoma group should be done. From the experiences of Levine and his associates [15] with the injection of turpentine plus cortisone, it has been suggested that much smaller quantities of cortisone be used for local injections. A series has been started using 0.025 to 0.25 mg. of cortisone injected into skin lesions. No therapeutic effects were noted in only eight patients.

14. Forsham, P. H.: Personal communication to the authors.

15. Levine, R.: Personal communications to the authors.

The important findings in the small series of patients in Table 3, with intradermal injections of cortisone, reveal the failure to inhibit the reaction to Pediculus humanus bite in a sensitive patient and the failure to prevent the development of a positive patch reaction. Recent studies [16] with compound F have shown definite local inhibition of the eczematous reaction, the tuberculin type of inflammatory response, and also local inhibition of the severe reaction to mosquito bites. To attempt to explain the difference between the reactions in the skin of animals and man, Levine suggests that in animal skin cortisone may be changed to compound F. From the standpoint of local therapy, the hypospray® instrument was preferred to the syringe and needle, since, in our experience, a single injection offers a broader distribution of material in the superficial portion of the skin. The instrument was used also in a few instances for the intramuscular injection of cortisone for systemic therapy.

CONCLUSIONS

Cortisone applied topically to the skin in ointment form in concentrations up to 750 mg. per 30 gm. of ointment produced no significant therapeutic responses in 114 patients, when the results were analyzed critically. Cortisone was also injected superficially into the skin by syringe and needle and by the hypospray® jet injection instrument. With both of these techniques a significant number of extensive inflammatory reactions in tissue were observed grossly, and even more frequently in the microscopic sections. In 65 patients receiving local injection of cortisone with the hypospray® jet injection instrument, a few striking results were observed, but these were not controlled. The various controls used at times in the study included the cortisone-free suspending mixture itself and also suspensions of cholesterol. A few experiments have been done with a water-soluble ester of cortisone. Initial experiments with the local injection of compound F show definite inhibition of both the local eczematous and the local tuberculin type of response. Further studies with the injection of compound F, and mixtures containing compound F, into the skin of man for diseases of the skin amenable to cortisone therapy are warranted, for, if there is any local action of compound F, injection rather than topical application should be more effective. For these studies, in which relatively superficial injections of the steroid are required, attempts should be made to reduce the local irritant quality of the suspensions now available.

441 Vine St. (Dr. Goldman).

16. (*a*) Goldman, L.; Preston, R., and Rockwell, F.: The Local Effect of Compound F on the Diagnostic Patch-Test Reaction, to be published. (*b*) Goldman, L.; Preston, R.; Rockwell, E., and Baskett, J.: The Inhibition of the Tuberculin Reaction and the Tuberculin Type of Inflammatory Response by Local Injection of Compound F, to be published. (*c*) Goldman, L.: A Controlled Study of the Local Effect of Compound F on the Severe Reaction to Mosquito Bites, to be published.

EXPERIENCE WITH A NEW ANTIPRURITIC AGENT

Preliminary Report on 1-(β-Dimethylaminoethoxy)-3-*n*-Butylisoquinoline Monohydrochloride

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THE OINTMENT herein evaluated, a new isoquinoline derivative incorporated in a bland base,[1] is a local anesthetic. In our appraisal of its antipruritic qualities in 128 cases, we have noted but one evidence of irritation and none of sensitization. It has proved to be effective in relieving the itching associated with various diseases of the skin, including some types which had seemed to be especially stubborn in our past experience. Summarized in the accompanying table are the diseases in which we have tested the new isoquinoline derivative as an antipruritic agent. (Note that no infectious diseases are included.) In all, the appraisal embraced the various types of pruritus, notably the anogenital group; localized neurodermatitis and lichen chronicus simplex considered together; various types of dermatitides other than the foregoing; a group of essentially chronic dermatoses, and a miscellaneous collection, unfortunately few in number, attached because of the use of the salve although somewhat beyond the original scope of the trial. The total included those patients who, having completed a satisfactory course of application of the ointment, permitted us an appraisal. This was believed to be sufficiently clear-cut to place them in a definite category. These patients had been instructed to apply the ointment as often as necessary to relieve itching, to a total of not more than five applications in 24 hours. It was to be used only for sensory relief and was to be discontinued when its purpose was accomplished. It was to be gently massaged into the affected part and covered or not as the situation appeared to demand. If no relief was obtained, the remedy was discontinued in two weeks; if benefit was noted, it could be continued as long as required. Some of our patients with pruritus ani have used it intermittently for 18 months. Some patients described the immediate effect as a mild burning for a minute or more followed by a numbing

Read at the Seventy-First Annual Meeting of the American Dermatological Association, Hot Springs, Va., May 26, 1951.

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1. Material for this study was supplied by Smith, Kline & French Laboratories, Philadelphia, under their code name SKF 538-A and as "quotane."

sensation in 5 to 10 minutes or longer. Often the burning occurred only at the initial application.

At first the active ingredient in its greaseless base was employed in a concentration of 0.15%. Although effective at this strength in the majority of patients, since no ill effects were observed, the strength was increased first to 0.3 and later to 0.5%. It has not been deemed necessary to raise it beyond this figure. No appreciable difference in antipruritic efficiency could be detected at these various concentrations, nor was any deviation observed when the composition of the base was changed to improve the pharmaceutical qualities of the ointment.

In anogenital pruritus (40 patients) there was usually fairly prompt relief. This was especially true in pruritus vulvae, in which of 20 patients (8 of them with

Results of Treatment of Dermatoses with SKF 538-A ("Quotane")

	Complete Relief	Improved	No Benefit	Total
Anogenital pruritus and noninfectious dermatitis				
Anal, scrotal, perineal, and combinations	6	10	3	40
Anal, vulvar, and combinations	8	11	2	
Pruritus of other regions				
Auricles, trunk, etc.	..	7	3	10
Neurodermatitis and lichen chronicus simplex				
Occipital, shoulder, neck, vulva	6	12	2	20
Dermatitis of various types (all noninfectious)				
Atopic	2	8	4	32
Contact	..	7	5	
Nummular	..	2	..	
Stasis	..	3	..	
Senilis	..	1	..	
Chronic dermatoses				
Psoriasis	..	6	1	16
Dermatitis herpetiformis	..	4	..	
Mycosis fungoides (premycotic)	..	..	1	
Lichen planus	..	4	..	
Miscellaneous				
Papular urticaria	..	4	..	10
Epidermophytid	..	2	..	
Cheilitis exfoliativa	..	1	..	
Neurotic excoriations	..	1	..	
Lupus erythematosus	..	2	..	
Seborrheic dermatitis	..	1	..	
Cicatrices	..	2	..	
Totals	22	85	21	128
Percentage of patients completely relieved or improved			84.4	

associated pruritus ani) only 2 were unimproved. One patient with kraurosis vulvae noted diminished itching, as did two patients with neurodermatitis vulvae.

Pruritus ani was almost always improved; in four of our patients complete relief was obtained: in only one was there no benefit. These patients, all of whom had been disappointed many times before by the failure of preparations of acknowledged value in such instances, did not anticipate significant help from the new remedy and accepted its use with scepticism. This attitude was entirely altered when the good effects were noted.

In three of four patients with chronic dermatitis of the scrotum, the ointment provided slight to great relief. This was particularly encouraging in view of the difficulties which we have met in the past in treating this condition with other antipruritic agents.

Next in importance to the success frequently achieved in the anogenital region was that obtained in the treatment of neurodermatitis (lichen chronicus simplex)

at the back of the head and neck. With one notable exception, the itching of 9 out of 10 patients was relieved by the ointment, 5 greatly or completely. All of the patients were women, some of whom had experienced little relief in years.

One eruption on which we tried the preparation with little hope for success proved unexpectedly yielding as far as the itching was concerned. This was dermatitis herpetiformis. Our experience was limited to four patients, but the ointment produced satisfactory results in all of them.

Itching of the auricles from causes other than pyoderma or other classifiable dermatoses usually gave way to the ointment. Here the condition was classed as a dermatitis of unknown origin or from contact. The ears were dry, red, scaly, and slightly swollen, no other part being affected. All of the six patients improved, although two only slightly.

Tested in several other itching conditions, the ointment produced some relief. The itching of atopic dermatitis was temporarily relieved by applications of the salve in 8 out of 12 patients, but the improvement was not always striking. One patient appeared to suffer irritation as a result of the application, our only instance of actual aggravation. Six patients with itchy psoriasis and four with lichen planus reported increased comfort, although no significant improvement in the appearance of the outbreak could be seen. To patients with assorted dermatoses the ointment did not give more than symptomatic encouragement. The few instances recorded carry little weight singly, but in sum they show an indication of the possibilities of further investigation of the effects of the application.

COMMENT

In evaluating this chemical in ointment base we were largely guided by the patients' expressions of relief, at times as strongly worded as their previous complaints of discomfort. Subjective though this evidence may be, it was especially convincing when uttered by a patient whose chronic itch had resisted many seemingly appropriate remedies. Spontaneous favorable remarks were frequently heard. It was not universally successful, however, nor did it cure the conditions for which it was used unless the abstinence of scratching permitted healing. It was a symptomatic relief rather than a cure.

In the section on treatment of pyodermas in the 1950 Year Book of Dermatology and Syphilology, Sulzberger and Baer [2] set up eight cardinal properties of agents for external use against infections of the skin. If we eliminate the first of these, dealing with effectiveness, etc., against micro-organisms, the other seven could be used as criteria in appraising antipruritic preparations. If we abbreviate and condense the other qualities under consideration, they will be found to present as good an evaluation of effectiveness against pruritus as against pyodermas: low capacity to elicit allergic reactions; no, or very low, irritancy or toxicity, local or general; not used for systemic administration; stable when employed in proper vehicles, and relatively inexpensive and acceptable to its users. In this final qualification, the authors, with picturesque alliteration, pass on various preparations

2. The 1950 Year Book of Dermatology and Syphilology, edited by M. B. Sulzberger and R. L. Baer, Chicago, The Year Book Publishers, Inc., 1951.

from the standpoint of whether they sting, stink, or stain. It is felt that the ointment discussed passes this test when appraised according to the seven standards, apart from the occasional mild initial stinging mentioned before.

SUMMARY

A new antipruritic topical application in ointment form was tried in the treatment of 128 patients with chronic itching eruptions and found to be effective in producing relief from itching in many cases. No sensitization and practically no primary irritation were observed.

136 S. Sixteenth St. (2).

527 Penn St. (Dr. Decker).

ABSTRACT OF DISCUSSION

Dr. Clarence S. Livingood, Galveston, Texas: Dr. Corson and his collaborators have reported the results of a careful and prolonged clinical investigative study, and we are indebted to them. All of us will agree that perhaps there is no clinical investigative project which is more difficult than the evaluation of an antipruritic agent.

Unfortunately, we have no satisfactory method of measuring pruritus or its alleviation in an objective manner, and in the evaluation of a given antipruritic agent the investigator is forced to depend on the statement of the patient who uses the preparation. The so-called paired comparison method of evaluating local medicaments, appropriately emphasized by Sulzberger and his group, is not particularly applicable to the study of antipruritic agents. Many factors influence pruritus, and the symptom is so variable from week to week, and indeed from day to day, that comparative studies of the antipruritic agent under investigation with other similar remedies and with the control vehicle are by no means entirely satisfactory. In our clinical investigation of antipruritic preparations we have attempted to form an opinion regarding the comparative effects of different ointments and lotions by asking the patient to use a given preparation for one week, then change it to another one for the next week, etc. However, this method also has limitations.

Our experience with this new drug is in general similar to that which Dr. Corson has reported. If you expect that this drug will effect prompt and complete relief of itching in all patients, you will be disappointed. On the other hand, if you anticipate that the ointment or the lotion containing this drug will be at least as effective in relieving pruritus as other so-called antipruritic agents, with the added very important advantage of having a comparatively very low irritation and sensitization index, then you will not be disappointed. We have used either an ointment or a lotion containing 0.5% of "quotane" in treatment of approximately 250 patients. For some of these patients the ointment or the lotion was continued for prolonged periods of time. Also it should be noted that many of these patients had had irritation and/or sensitization reactions to previously applied medicaments. It seems significant that we have not noted a true sensitization reaction to the drug in a single patient, although five of these patients had significant irritation at the treatment site. On patch testing and on subsequent reapplication of the ointment base without the drug, it appeared that the irritation in these patients was due to the vehicle rather than to "quotane." Perhaps prolonged additional experience will establish a significant sensitization index, but thus far "quotane" seems to occupy a very favorable position in this regard. In vitro studies in tissue culture experiments which we have done, as well as experiments which we have conducted with a closed patch-test technique, lead us to believe that "quotane" occupies this favorable position in respect to irritation because it is used in a 0.5% concentration rather than the 1 to 5% concentrations which are employed in the preparation of many other available antipruritic topical agents, such as phenindamine (thephorin®) phosphate ointment, tripelennamine (pyribenzamine®) hydrochloride ointment, dibucaine (nupercaine®) hydrochloride ointment and cyclomethycaine (surfacaine®) ointment. Fortunately the results with the 0.5% concentration of "quotane" in an ointment base or in a lotion vehicle are at least as good as those which we obtain with the use of other topical medicaments with 1 to 5% concentrations.

It seems doubtful to me that a completely effective topical medicament for the relief of pruritus will ever become available. Nevertheless it is necessary for us to use the best available local treatment for patients with pruritic skin diseases. In selecting the topical medicament, it is of paramount importance to consider the matter of possible irritation and/or sensitization reactions. With these considerations in mind, and on the basis of experience accumulated to date, it seems probable that this drug will be a valuable addition to our therapeutic armamentarium for the local treatment of pruritus.

Dr. Francis W. Lynch, St. Paul: In "quotane" lotion the manufacturers have incorporated menthol and camphor which, of course, leads to major difficulty in evaluating a new drug. For investigational use the ointment contained only "quotane," and the base alone was available for comparison of its effect. I would like to corroborate the statements made by Dr. Corson and Dr. Livingood, having used the drug in about the same number of cases as Dr. Livingood. We had one patient with proved sensitization due to the base and not to the active drug. We too had patients use the ointment for a long time, many months, without sensitization developing. The duration of the antipruritic effect has been very satisfactory. Many patients have applied the drug upon retiring at night, and relief was maintained throughout the night.

The control base, without the active drug, was used by 15 patients, and I think that we are satisfied that it is the drug that is effective, although the base is pleasant and soothing. We used the drug in the treatment of 18 patients with contact dermatitis in order to see whether it was well tolerated, and we found it to be tolerated just as well as in any other group of patients. We used it in moist dermatitis and found it well tolerated. Just as in the case of Dr. Corson, our most satisfying results appeared in anogenital pruritus and localized dry neurodermatitis (lichen chronicus simplex).

Dr. James Mitchell, Chicago: At the San Diego meeting of the American Dermatological Association, I listened with great enthusiasm to a discussion by Dr. Shelmire on the effectiveness of phenindamine (thephorin®) phosphate ointment. Returning to Chicago I had my name added to the list of experimenters, and I was supplied with a goodly amount of the ointment. At first the results were very satisfactory, but later the drug proved to be a sensitizer, and I have had no end of trouble since that time. Reactions to all patch tests, prior to the use of the ointment, have been negative, and all severe reactions have resulted from a prior use or a sensitizing period of the ointment. Tripelennamine (pyribenzamine®) hydrochloride cream and methapyrilene (histadyl®) hydrochloride cream, particularly with cyclomethycaine (surfacaine®), have also been great troublemakers.

Dr. Donald Pillsbury, Philadelphia: We also have done some work with this compound during the past 18 months, and like Dr. Corson we have been dissatisfied with many of the available antipruritic substances, particularly on the basis of their sensitizing capacity. We have now treated some 700 patients with this compound in varying concentrations, and in approximately 150 of the patients we have attempted to do it on a controlled basis. I do not know of any clinical experiment which is more difficult, however, because in evaluating the relief from itching one has no satisfactory method of measurement.

A few general statements are worth keeping in mind in regard to antipruritics. With the exception of a few compounds, such as histamine, almost anything one puts on the skin relieves itching in a certain number of patients. The minute one starts to do a controlled study of an antipruritic, one is impresesd with the effectiveness of many simple ointment bases in relieving the itch.

This particular compound has a local anesthetic potency of about five times that of dibucaine hydrochloride, and the molecule has no relation to procaine hydrochloride at all. Shelley and Melton some two years ago did a rather exhaustive survey of the literature, and they found reports on some 57 different antipruritic agents. There were no controlled studies at all. It was very difficult to evaluate these reports, and, therefore, it has been difficult to evaluate the relative effectiveness of new antipruritics in comparison with old compounds.

Since then there have been two or three studies on antipruritics in which controls have been observed. Our experience with "quotane" has been that the compound is not effective from

the antipruritic standpoint in concentrations of less than 0.2% and 0.5% seemed to be the optimum. There is some evidence that 1% is a mild primary irritant.

In the control series—and these figures are always relative—we found that 65% of the patients seemed to get a reasonably satisfactory degree of relief of itching from the base alone, while the base plus the "quotane" in a strength of 0.5% produced some relief of itching in 88% of the patients. We have to date seen no instance of sensitization. We have treated patients for as long as 18 months. I think it is a useful preparation, as Dr. Livingood has pointed out. It does not relieve itching in every patient, but it seems to do so in a satisfactory percentage of patients, and as yet without any evidence of significant sensitizing effects.

Dr. Robert Gilman, Philadelphia: At U. S. Naval Hospital, Philadelphia, we, too, have had occasion to use this new antipruritic, although not to the extent that Dr. Pillsbury reports. Our preparation was in both the 0.15 and 0.3% strengths, and the only near irritation that might be interpreted as possible sensitization was in the reaction to one control patch test. Our results were surprisingly good even in those instances in which ointment forms are generally avoided.

I should like to add another use for the drug besides those mentioned by the speaker and discussers, and that is in herpes zoster. We used it in a number of patients with no adverse effects, and in all instances the itching, pain, and burning were relieved. Our experience is, of course, subject to the constant variable and difficulty of control in patient-testing of new drugs. The average patient, when he knows that he may be getting something new—and he is quick to detect it—believes that full cooperation with the doctor usually implies a favorable response on his part. We must continue to view our results as objectively as possible.

Several patients did complain of the drying effect of the vehicle. These were usually older men with chronic conditions. The remainder tolerated it very well, and we feel that the preparation is a worthwhile contribution. I believe that the drug was originally intended for topical use for local anesthesia on mucous membrane surfaces, such as in cystoscopy, and that the preparation in ointment form for skin application was intended to determine some index as to its sensitization properties. This has indeed been at a minimum, and from what I gather from Dr. Corson and others we had best keep within the suggested 0.5% strength.

Dr. Lynch's comments about the lotion, which I have seen and used sparingly, are cogent. The addition of two or three other antipruritics would seem complicating and unnecessary.

Dr. J. Lamar Callaway, Durham, N. C.: I have used "quotane" lotion and "quotane" ointment on more than 300 patients with good results and without any proved example of primary irritation or sensitization. Examples of sensitization may develop in the future but have not been observed to date in my experience. I feel that "quotane" ointment and lotion are as effective as any of the conventional antipruritics in use. Dr. John Dees at Duke Hospital has been using this preparation for some two years as a local anesthetic for cystoscopic operations. He has not, as yet, noticed any evidence of sensitization.

Dr. Erwin P. Zeisler, Chicago: Not being in practice and not having any clinical material at my disposal, I cannot express an opinion about a new antipruritic drug. Unfortunately, the list is already a large one, and the introduction of a new agent complicates rather than clarifies the situation. It seems to me that we sometimes forget the old and well-established therapeutic remedies in favor of newer and untried ones. For instance, my father, from the time he came to Chicago in 1880 until his death in 1919, used continuously and with great satisfaction, an antipruritic lotion containing as its solid constituents bismuth subnitrate and zinc oxide, the formula of which I have given your secretary. This was often combined with the use of an ichthammol ointment at night, the two together securing better results in controlling pruritus and in healing such troublesome disorders as the different forms of eczema. This treatment is not, of course, applicable to generalized or senile pruritus, as it is too drying. In rebellious pruritus, I found the addition of 3 to 5% crude coal tar to the ichthammol mixture of definite value. It seems to me that whenever you have to use a preparation for as long as one and one-half years, as Dr. Corson did in one case, it would be better to cast around for another more effective remedy.

I might mention in this connection that, even if you are not in practice and have an analytic mind, you occasionally may stumble on a therapeutic suggestion that is valuable in medicine. I recently sent to the American Medical Association a suggestion for a new treatment for burns which they found sufficiently interesting to refer to their Council on Pharmacy and Chemistry.

DR. EDWARD F. CORSON, Philadelphia: The experiences of the discussers have been so much broader than mine that I feel as though I were carrying the small end of the load. I appreciate the fact that they have followed more or less along the same line that I pursued. I would add that at one time the manufacturer put menthol and camphor in the preparation; right away patients noticed the odor, and some said, "I have had this stuff before." It seemed to me a confession of weakness to add old-time antipruritics to the presumably important ingredient. The manufacturer has now dropped the aromatics mentioned.

TINEA CAPITIS CAUSED BY TRICHOPHYTON TONSURANS (SULFUREUM OR CRATERIFORME)

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MEDICAL mycology has enjoyed a tremendous wave of popularity in recent years, especially among dermatologists. The appearance about 10 years ago of the epidemic (human) type of preadolescent tinea capitis in the United States and its subsequent rapid spread throughout the majority of its cities necessitated the adoption of culture methods as a routine in all diseases involving the scalp, in order that the prognostic, therapeutic, and epidemiologic status of each case could be correctly assessed. These extensive cultural studies have also disclosed a surprising number of cases of other varieties of scalp infection heretofore considered rare, and interesting variations in the geographical distribution of certain species of infecting fungi are becoming apparent.

The present communication deals with the discovery that infection of the scalp by the fungus Trichophyton tonsurans is now by no means rare in the children of Texas and California and is even encountered occasionally in adults. Whether this represents an actual increase in the frequency of the disease or connotes simply that such cases were previously unrecognized is not clear. The rarity of reports in the literature suggests the former.[1] Since our attention has been directed toward this infection, we have been able to prove its presence by microscopic and cultural methods in many cases which formerly would have been considered clinically so typical of other nonfungous disorders that laboratory assistance would not have been sought.

During the past three to four years we have observed 37 cases of tinea capitis in children and 7 in adults in which the organism proved culturally to be T. tonsurans. Although this is not a large number of cases, it is larger than any previously reported series, and it justifies the publication of the following preliminary study.

Read before the Section on Dermatology and Syphilology at the One Hundredth Annual Session of the American Medical Association, Atlantic City, June 15, 1951.

1. (*a*) Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, Ed. 3, Chicago, The Year Book Publishers, Inc., 1949, pp. 48 and 50. (*b*) Benedek, T., and Felsher, I. M.: Epidemiology of Tinea Capitis, Arch. Dermat & Syph. **49**:120-123 (Feb.) 1944. (*c*) Levin, O. L., and Behrman, H. T.: Problem of Non-Fluorescent Ringworm of Scalp, J. A. M. A. **128**:350-352 (June 2) 1945. (*d*) Steves, R. J., and Lynch, F. W.: Ringworm of Scalp: Report of Present Epidemic, ibid. **133**:306-309 (Feb. 1) 1949.

It is known also that others have recently observed this disease in increasing quantities in the states bordering on Mexico and that the incidence in Mexico itself has risen so sharply that almost all tinea capitis is now of this type.

It seems appropriate to consider these facts as a warning, at least, that an epidemic invasion is in process. Until more is known of the mode of transmission of the infection, it seems likely that it may spread over the continent from the Southwest as did the type due to Microsporum audouini from the East in 1940.

CLINICAL MANIFESTATIONS

Scalp infections caused by T. tonsurans differ in many respects from those due to species of Microsporum. The former should be suspected when the involved plaques tend to be angulated or polygonal rather than rounded, when the hairs are seen to be broken off so close to the surface of the scalp that they appear as black

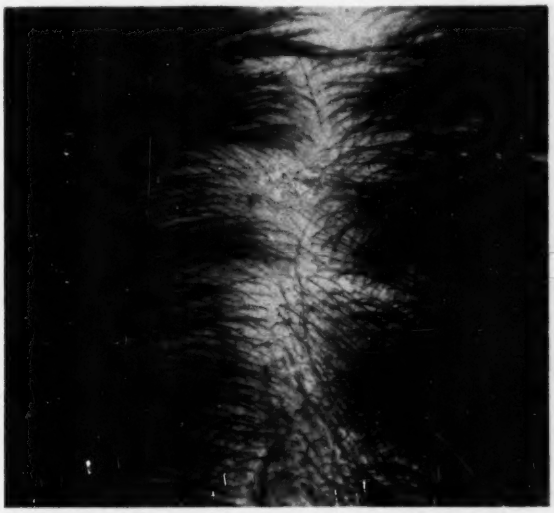

Fig. 1.—Small scaly patch of tinea capitis resembling seborrhea. Fungi were demonstrated easily by microscopic examination (sodium or potassium hydroxide preparation). This represents the epidermal phase of infection.

dots, and when the infection is unduly prolonged or continues after puberty. The phenomenon of fluorescence is almost uniformly not observed, the direct microscopic examination of involved hairs reveals endothrix infection, and the culture yields an easily differentiated growth.

The clinical course of any single plaque of the disease usually includes three stages which lend themselves to separate discussion, although all three stages are usually present simultaneously in the same patient.

A. *Epidermal Phase.*—In the epidermal stage (Fig. 1) the infection is limited to the epidermis and has not reached the pilus. Clinically the scalp presents a few or many small patchy areas resembling seborrheic dermatitis. Unless one maintains a high index of suspicion for tinea capitis, such scaly areas may not be examined for the presence of fungi, and the diagnosis will then be missed. The infection is very pruritic, and excoriations are usually present. This epidermal stage of infection may often be observed at the periphery of an old lesion which is healing in the center.

The seborrhea-like areas may be dry or oily depending somewhat on the degree of oiliness of the scalp being invaded. A gray, erythematous, or brownish color may characterize the scaly patches. The scalp may be involved in a few areas only, but usually many are present. Extension to the neighboring glabrous skin occurs as a patchy ill-defined eczematoid eruption rather than as a typical tinea circinata. Invasion of one or more nails has been observed, possibly resulting from scratching the scalp. A single circinate lesion [2] of the knee was found in association with tinea capitis in one adult.

When the scalp alone is involved, the epidermal phase must be differentiated principally from seborrheic dermatitis. Examination of potassium hydroxide preparations microscopically and cultural studies will either confirm or rule out the possibility of tinea capitis. The presence of seborrheic dermatitis or psoriasis on areas other than the scalp usually favors that diagnosis also for the scalp disease.

B. *Follicular Invasive Phase.*—The infection progresses continuously from the epidermis to the follicle, thence to the hair shaft and root. After invasion of the cortex of the hair, friability and fracture of the pilus take place readily. The course of the infection is slow, with involvement of a few hairs at a time. Within a few weeks after the invasion of a new site, however, broken hairs can be found. Such involvement of the hairs soon produces small areas of alopecia, exhibiting in adults atypical or unusual shapes, some finger-like, some roughly rectangular, and others oval in pattern but having irregular borders. The areas of alopecia vary in diameter from 0.25 cm. or less to as much as 5 cm. In contrast to Microsporum infections, the areas of baldness frequently contain a sprinkling of normal, full-length, uninvolved hairs. The length of the broken hairs is variable and fracture of the hair generally occurs at the level of the scalp, producing a "black dot" appearance (Fig. 2). However, infected hairs measuring approximately 3 cm. in length are occasionally observed.

Folliculitis is characteristically present in the most active portion of any plaque, usually near the periphery; associated pyogenic infection results in crusting. Kerion develops frequently, especially in children,[3] and the appearance resembles that seen in Microsporum infections.

Lewis [4] states that under Wood's light the infected hairs may have a dull gray fluorescence. This phenomenon was observed in only one of our patients, an adult, a factor which rendered manual epilation much easier. Even the "black dot" hairs could be removed successfully in a high percentage of tries in this patient. In the other patients manual epilation was tedious, time-consuming, and partially unsuccessful even under magnification. Neither Seale [5] nor Lehmann and Pipkin [6] observed fluorescent hairs in studying their cases of T. tonsurans.

In this phase there is a close clinical similarity between T. tonsurans infections and the other endothrix types of tinea capitis (Fig. 3), especially that due to T.

2. Slaughter, J. C., and Cawley, E. P.: Infection of the Glabrous Skin Instigated by the Fungus Trichophyton Sulfureum: Report of Case, J. Invest. Dermat. **9**:63-64, 1947.

3. Moore, M., and Wooldridge, W. E.: Kerion Caused by Trichophyton Sulfureum, Arch. Dermat. & Syph. **61**:460-465 (March) 1950.

4. Lewis, G. M., and Hopper, M. E.,[1a] p. 63.

5. Seale, E. R.: Personal communication to the authors.

6. Lehmann, C. F., and Pipkin, J. L.: Personal communication to the authors.

violaceum and the superficial form of favus. Cultural studies are generally essential for their differentiation. In a teen-age girl with T. tonsurans infection observed by Shelmire,[7] little or no inflammatory reaction was present, simulating alopecia areata. After close inspection with a magnifying glass, however, broken hairs were obtained for culture, and the specific diagnosis of tinea capitis was made.

When pustules are present, they are often seen at the periphery of the bald area associated with "black dot" hairs in a manner simulating folliculitis decalvans. The specific diagnosis depends upon microscopic examination of the involved hairs and scales as well as upon cultural studies.

The Healing Phase.—When healing takes place in any one area, it is usually because the infected hairs have left the follicles, either spontaneously, as a result of treatment, by epilation, or through the development of kerion. Healing is frequently

Fig. 2.—Area of baldness demonstrating the pattern of alopecia. Note the sprinkling of "black dot" hairs.

observed in the central portions of involved plaques, even while at the periphery the infection is still actively progressing. After a few weeks, normal hairs begin to be visible in these areas, and the appearance quickly returns to normal. Permanent thinning of the hair is infrequent unless kerion was present with resulting atrophic scarring. Reinfection in the center of a healed plaque has been observed occasionally.

The foregoing discussion portrays the disease as it occurs in children. In exceptional cases the infection may be prolonged for years, even extending beyond puberty, in contrast to the usual observation in Microsporum infections. Development of the disease in the adult scalp has been observed by Shelmire,[7] Lehmann and Pipkin,[6] Seale and Richardson,[8] Lewis,[9] Eppright and McCuistion,[10] and Kligman

7. Shelmire, B.: Personal communication to the authors.
8. Seale, E. R., and Richardson, J. B.: Personal communication to the authors.
9. Lewis, G. M.: Personal communication to the authors.
10. Eppright, B. R., and McCuistion, C. H.: Personal communication to the authors.

and Constant.[11] The clinical course in all cases paralleled the childhood type in its less severe forms, excepting in two of Lehmann and Pipkin's patients, in whom it resembled discoid lupus erythematosus. Three of the infections in adults also resembled mild childhood forms without kerion or the development of much atrophic scarring. However, a severe persistent kerion was observed in a fourth patient, an

Fig. 3.—Section from an active lesion showing endospores in the hair root and a dense mantle of cellular infiltrate about the follicle; hematoxylin and eosin; × 125.

80-year-old woman, but no permanent scarring or alopecia resulted. Permanent alopecia with or without atrophy is not an uncommon sequel of the infection in adults.

Two patients observed by us presented a different clinical picture that is worthy of separate discussion.

11. Kligman, A. M., and Constant, E. R.: Family Epidemic of Tinea Capitis Due to Trichophyton Tonsurans (Variety Sulfureum), A. M. A. Arch. Dermat. & Syph. **63**:493-499 (April) 1951.

TRICHOPHYTON TONSURANS INFECTION OF THE ADULT SCALP RESEMBLING LUPUS ERYTHEMATOSUS

Two of our adult patients with infection of the scalp exhibited a stage in which the clinical appearance simulated lupus erythematosus [12] so closely that several excellent dermatologists accepted the latter diagnosis, while others averred that both diseases must be present simultaneously (Figs. 4 and 5). In both instances the involved areas became erythematous soon after alopecia developed. The erythema did not extend beyond the limits of the infected area, and it persisted for months, even after the infection had apparently healed. A varying degree of surface scaling, atrophy, and telangiectasia was present, lending additional support for the diagnosis of lupus erythematosus. However, infiltration was not palpable, and true stippling, follicular plugging, and dilated follicular openings were not observed. The discovery of a few typical "black dot" hairs near the periphery of the involved areas furnished

Fig. 4.—Area of infection by Trichophyton tonsurans resembling discoid lupus erythematosus.

a clue, and such hairs when extracted and examined under the microscope revealed fungus elements within the hair shafts. Cultures yielded colonies typical both grossly and microscopically of T. tonsurans, variety sulfureum.

This unusual clinical entity has not been reported previously as far as we can discover. It has not been observed in children. Lehmann and Pipkin,[6] however, have seen two patients who exhibited many features similar or identical to ours.

The features useful in the differential diagnosis between lupus erythematosus and T. tonsurans infection of the scalp are presented in the accompanying table.

Following in the wake of this type of scalp infection were atrophic areas of a pale flesh color, slightly depressed, permanently devoid of hair, and with a smooth shiny surface. Scaling, telangiectasia, and a gradual fading of the long-standing erythema were observed. "Burned out" areas with atrophy were noted in association

12. Dr. Bedford Shelmire allowed us to study and report one of his cases of lupus-erythematosus-like tinea capitis.

with active patches of tinea capitis in varying phases of development or healing. In the cicatrizing variety of T. tonsurans infection there seems to be a tendency for spontaneous healing and "burning out" of the process locally after a period of months or years. The atrophic phase (Figs. 6 and 7) must be differentiated from the terminal stages of lupus erythematosus and folliculitis decalvans, from alopecia cicatrisata, and the end-stage of favus and other endothrix Trichophyton scalp infections. In certain cases a differentiation is almost impossible without prolonged and close observation. The history of the development of atrophy and perhaps the persistence of active areas of tinea capitis would be of aid in differentiating atrophic T. tonsurans from alopecia cicatrisata. In the late stages of folliculitis decalvans great difficulty would be encountered in making a differential diagnosis. The history of an earlier suppurative folliculitis would favor the possibility of folliculitis decalvans, although a mild pustular folliculitis was observed in the two patients with T. tonsurans infection resembling discoid lupus erythematosus. The presence of lupus erythematosus lesions on the ears, retroauricular sites, or face, accompanying the involvement of the scalp, would be of distinct help in making the diagnosis.

Differential Diagnosis Between Lupus Erythematosus and Trichophyton Infection of the Scalp

Lupus Erythematosus	Trichophyton Tonsurans Infection
1. Fixed erythematous patches	1. Fixed erythematous patches
2. Infiltration palpable	2. Infiltration slight or absent
3. Telangiectasia	3. Telangiectasia in some patches
4. Follicular plugs, stippling, and carpet-tack scales	4. No follicular plugs
5. Alopecia	5. Alopecia
A. Oval and patterns with irregular outlines	A. Finger-like and rectangular areas of alopecia in addition to oval areas
B. Hairs usually not present within the involved areas	B. A few normal hairs may be noted in the areas of involvement
C. No "black dot" hairs	C. "Black dot" hairs occasionally seen
6. Atrophy with depigmentation or hyperpigmentation	6. Atrophy

MYCOLOGY

The status of species delineation within the genus Trichophyton is still controversial, in spite of the fact that during recent years tremendous progress has been made towards clarification. Much study will be necessary before these species, admittedly belonging to the "crateriforme group," [13] can be considered to be fully understood; such investigations are known to us to be in progress by at least two competent investigators [14] from whose opinions the following conclusions have been derived.

From 17 species names included currently in the crateriforme group of Trichophyton under four headings, only 3 appear to be assigned to fungi newly isolated from human infections in the United States: sulfureum, crateriforme, and tonsurans. Specimens identified by one of these names in the opinion of one mycologist have received other designations by equally competent colleagues. It is a fact that there is a great deal of variation in gross and microscopic appearance of cultures of these fungi; even among "daughter" colonies of the same parent culture grown on the same medium under identical conditions, the widest possible variation consistent with crateriforme grouping can be observed.[14]

13. National Research Council, Division of Medical Science: Manual of Clinical Mycology, prepared by Conant, N. F., and others (Military Medical Manual), Philadelphia, W. B. Saunders Company, 1944.

14. Plunkett, O. A., and Georg, L.: Personal communication to the authors.

On purely clinical grounds there seems to be little or no necessity of differentiating between the crateriforme group of fungi; all are capable of causing the clinical syndrome discussed in this paper. It is admitted, however, that the group itself must be kept apart from other trichophytons both on clinical and mycologic grounds.

At present it seems wise to await more studied conclusion on this subject. Meanwhile it is acceptable to many of those interested in the subject to use the designation Trichophyton tonsurans (Malmsten, 1845) for the entire group because of priority, utilizing the terms "sulfureum," "crateriforme," and perhaps "acuminatum" to describe varieties if they seem appropriate and necessary.

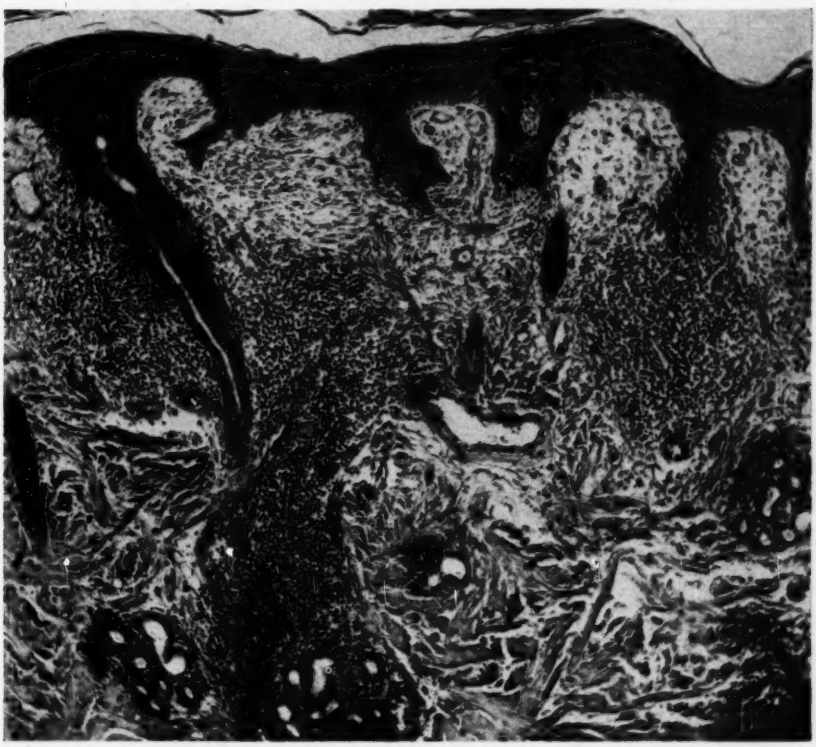

Fig. 5.—Section from the preauricular patch showing acanthosis of the rete pegs, edema of the papillae, and a dense cellular infiltrate about the sweat ducts and sweat glands; hematoxylin and eosin; × 94.

Potassium hydroxide preparations of epidermal scales from sites infected with these fungi do not differ significantly in appearance from those derived from other dermatophytoses; there is perhaps a little more tendency toward rounded arthrospores in chains. When hair shafts are invaded, the majority of the fungous elements are seen to lie within the hair (endothrix involvement) and consist of hyphae and chains of rounded arthrospores. The air bubbles characteristic of favus have not been observed.

Cultures have yielded colonies exhibiting an irregularly elevated and indented surface, velvety to powdery in appearance, with a color varying from dull yellow

(sulfureum variety) through dark buff to brown. Older colonies frequently develop white, cottony pleomorphic tufts of mycelium. The reverse of the colonies as seen through the medium exhibits a brown coloration with a reddish-purple tinge when young, becoming dark brown with age.

The organisms recovered from those infections clinically simulating lupus erythematosus did not differ from the rest of the series.

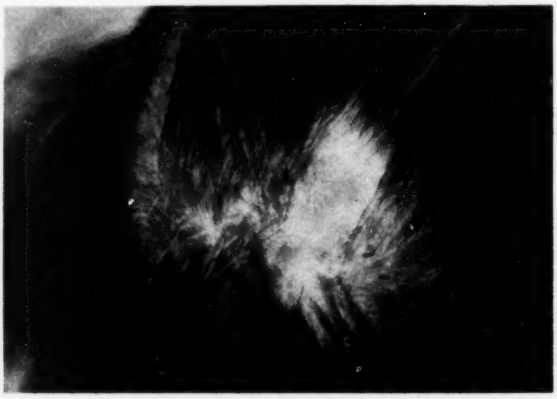

Fig. 6.—End stage of the infection in this local area depicting atrophy and permanent baldness.

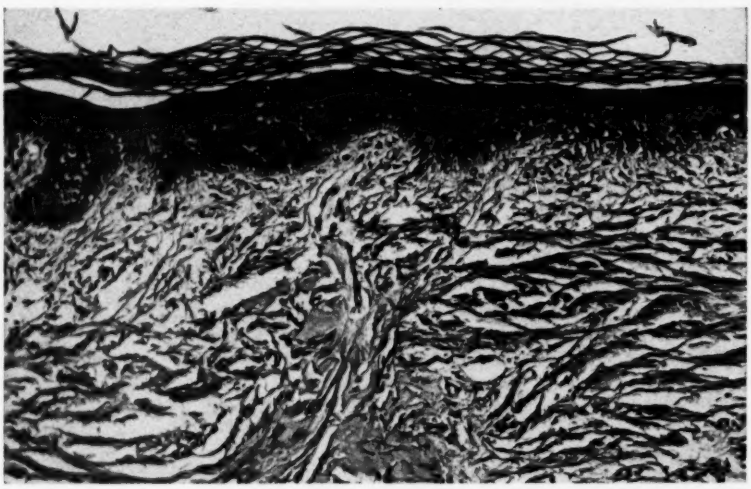

Fig. 7.—Section from an atrophic patch showing a thin loose scale, atrophic epidermis with intracellular edema, edema of the corium, and a mass of senile elastosis in the mid corium; hematoxylin and eosin; × 125.

HISTOPATHOLOGIC FINDINGS

Biopsies were performed on lesions that bore a gross resemblance to those of chronic discoid lupus erythematosus, on patches of active tinea capitis, and on areas that had undergone involution and atrophy.

A section taken from a preauricular patch that simulated lupus erythematosus clinically (Figs. 4 and 5) showed no histopathologic features of that disease. There was a thin crust overlying a scale which contained areas of parakeratosis. There was a diffuse intercellular edema in the epidermis, and the rete pegs showed active acanthosis with numerous mitotic figures. The papillae were long and broad, and they were the site of intense edema and diffuse vascular dilatation. There was a slight cellular infiltrate in the papillary layer, but deeper in the corium about the blood vessels, sweat ducts, and sweat glands there were circumscribed dense masses of cellular infiltrate containing many plasma cells, lymphocytes, histiocytes, and polymorphonuclear leucocytes. The edema extended deeply into the corium.

A section taken from the same patch two years later showed an atrophic epidermis covered by a parakeratotic scale. In the upper corium there were several dense foci of cellular infiltrate that extended up to the epidermis. In these foci the

Fig. 8.—Tinea circinata on thigh of same patient. Fungi were found (sodium hydroxide preparation).

predominant cells were lymphocytes, but a few histiocytes and plasma cells were also seen, and an occasional giant cell. The intervening parts of the upper corium showed edema and vascular dilatation.

A section from an area of active tineal infection on the vertex showed a flat atrophic epidermis with intense intracellular edema distributed throughout all layers. In the upper corium there was considerable edema, and the blood vessels were dilated. In several follicles the hair root was filled with long columns of endospores, and about these follicles were loose masses of lymphocytic infiltrate. A section taken from another active patch of tinea capitis in this patient showed a parakeratotic scale, intracellular edema throughout the epidermis, intense edema throughout the corium, invasion of the hair roots by endospores, and dense mantles of cellular infiltrate about the blood vessels adjacent to the affected follicles.

A section from an active patch in our second patient in whom the infection simulated lupus erythematosus showed a thin, loose scale (Fig. 3). The epidermis

showed slight acanthosis, while the corium was edematous and the seat of vascular dilatation with a slight perivascular infiltrate. Within the hair root there were several columns of endospores, and the follicle was surrounded by a circumscribed dense mantle of infiltrate containing lymphocytes, histiocytes, and connective tissue cells.

A section from a "burned out" patch on the scalp (Figs. 6 and 7) showed a flattened atrophic epidermis with a thin loose scale. The granular layer was intact, and there was intracellular edema throughout the epidermis. There was diffuse edema throughout the corium, but it was most marked in the subepidermal layer. In this zone there were also small accumulations of slight cellular infiltrate. A few sweat glands could be seen, but hair follicles and sebaceous glands were absent. In the mid corium there were several poorly defined masses of senile elastosis.

Even though clinically some of the lesions simulated those of lupus erythematosus, the histiopathologic features were sufficiently distinctive to warrant an unqualified differentiation between the two diseases. In sections taken from active lesions, areas of parakeratosis in the scale, active acanthosis of the rete pegs, intracellular and intercellular edema throughout all layers of the epidermis, and the great number of plasma cell and polymorphonuclear leucocytes in the infiltrate all spoke against any possible confusion with lupus erythematosus. The presence of endospores within the hair roots was decisive in making an absolute histopathologic diagnosis of tinea capitis. In the atrophic stage, however, a definite causative histopathologic diagnosis could not be made. Many of the destructive diseases that affect the scalp produce as their end-result the same histopathologic picture. In sections from our patients, however, there was one feature that suggested that the causative disease had not been lupus erythematosus. The masses of senile elastosis here were located in the mid corium, while in lupus erythematosus this feature is generally seen in the subepidermal layer.

EPIDEMIOLOGY

The source of this infection has not been directly traced to animals, although they must still be suspected. Barber and beauty shops are likely sources of spread of the infection. Direct proof of transference from one human being to another is only occasionally obtained. One patient observed apparently transmitted the disease to her grandson. Family epidemics are being discovered with increasing frequency. Seale [5] observed two infected playmates who lived on opposite sides of the street. However, manual epilation was carried out at intervals for 18 months by the daughters of one of our patients without transmission of the disorder.

Sex Incidence.—In children we observed T. tonsurans infections equally between the sexes or slightly more commonly in boys than in girls. In adults all of the infections which we observed and those diagnosed by colleagues with two exceptions have been in women. Pipkin [15] and Seale [5] each have treated an adult male with tinea capitis caused by T. tonsurans.

Age of Adults.—T. tonsurans infection may have its onset at any age. It has been observed to persist past puberty. It has been known to have been present before, during, and years after the menopausal period. In this respect and in its lengthy course it is comparable to favus and to infection by T. violaceum. It is the exception for Microsporum lanosum and M. audouini infections to persist or develop after puberty.

15. Pipkin: Personal communication to the authors.

THERAPY

It is reasonable to assume that there are mild cases of tinea capitis due to T. tonsurans, particularly in children, in which spontaneous healing may occur. In such cases the infection "burns out" in time with or without the assistance of topical therapy and/or epilation. There is doubt that the infection in adults ever heals spontaneously or "burns itself out." Lehmann and Pipkin [6] have one patient in whom the infection has persisted from the age of 7 or 8 to the present age of 63 years.

Topical therapy appears to be of questionable value. When kerion occurs, healing generally follows within a few weeks. Manual epilation is very difficult, since most of the hairs are broken at the surface of the scalp. In one adult patient, in whom the infected hairs exhibited fluorescence under Wood's light, manual epilation could be done satisfactorily. However, a "cure" has not yet been accomplished in this case.

Lehmann and Pipkin [6] have had wide experience in treating tinea capitis due to T. tonsurans, and they have found x-ray epilation to be the treatment of choice in both children and adults. This should be followed by the manual removal of every hair which is not shed following the x-ray epilation.

In adults x-ray epilation may be followed by a persistence of the infection. A second epilation was known to have been necessary in three patients and in addition manual removal with forceps and a Hagedorn needle employed for the "black dot" hairs. X-ray epilation alone is, therefore, more likely to fail here than in patients with tinea capitis due to M. audouini.

SUMMARY AND CONCLUSIONS

Tinea capitis caused by the fungus Trichophyton tonsurans (variety sulfureum or crateriforme) has been observed with ever-increasing frequency in the past few years in Texas and California. It seems reasonable to predict that an epidemic invasion is in process, originating in Mexico and entering the United States by way of the bordering states. The epidemiology is not as yet clear but must be suspected to be of the anthropophilic type so likely to result in extensive spreading, especially among city children.

The infection is encountered occasionally in adults, usually women; it may persist for many years without healing at puberty.

This organism produces a "black dot" type of tinea capitis, similar to that due to Trichophyton violaceum; kerion formation is common. In mild cases the patches may be mistaken for seborrheic dermatitis; the degree of pruritus helps in differentiation. Involved areas frequently have a distinctive angulated, irregular, polygonal form. Fluorescence is usually lacking, hence filtered ultraviolet radiation cannot be used for exclusion.

Two cases which closely simulated discoid lupus erythematosus clinically are described. The histopathologic features of value in differentiation are emphasized.

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EXPERIMENTAL STAPHYLOCOCCAL FOLLICULITIS

Comment on Its Possible Relationship to Acne

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SYDNEY, AUSTRALIA

IN A PREVIOUS paper [1] I described the way in which the experimental incubation of staphylococci on the skin gave rise to a variety of poral lesions which, in the case of the sweat pores, resembled bullous impetigo and miliaria rubra. Brief mention was made of the fact that these same experiments gave rise to follicular lesions, namely, follicular impetigo (Bockhart), acneform pustules, and abortive furunculosis.[2] My purpose in this paper is to describe and discuss these follicular lesions in more detail.

PROCEDURE

Staphylococci grow abundantly on nutrient agar containing 8% by weight of sodium chloride ("salt agar"), whereas bacteria of most other genera are inhibited or destroyed.[3] This selective property of salt agar was used to induce pure staphylococcal infection of the skin in the following manner. (Fuller details are given in the earlier paper.[1])

Nine normal volunteers were selected, and to each were strapped two moulded aluminum cups filled to the brim with the agar preparation. The agar in one cup (the test cup) was inoculated with a strain of Staphylococcus aureus,[1] while the agar in the other cup (the control cup) was kept sterile by the incorporation of thimerosal N. F. (merthiolate,® Eli Lilly & Company).

The cups were left in place for a period of from 5 to 10 days so as to produce responses on the test side. In two experiments, biopsy specimens were taken from the test side 24 hours after removal of the cups. More than 1,000 serial sections were made and examined.

CLINICAL RESULTS

As a result of 24 separate experiments, the test side disclosed a total of four definite follicular responses. These were made up of superficial pustular folliculitis (two instances) and superficial pustular folliculitis associated with early furunculosis (two instances). Lesions at the sweat pores frequently coexisted, as already described.[1]

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1. O'Brien, J. P.: The Etiology of Poral Closure: An Experimental Study of Miliaria Rubra, Bullous Impetigo and Related Diseases of the Skin, J. Invest. Dermat. **15**:95 (Aug.) 1950.

2. O'Brien,[1] Fig. 25.

3. Hill, J. H., and White, E. C.: Sodium Chloride Media for the Separation of Certain Gram-Positive Cocci from Gram-Negative Bacilli, J. Bact. **18**:43 (July) 1929. Koch, F. E.: Elektivnährboden für Staphylokokken, Zentralbl. Bakt. (Pt. 1) **149**:122 (June 30) 1942.

Since follicular papules cannot always be readily distinguished from papules at the sweat pores, the estimate of follicular responses is probably too low. Moreover, additional lesions, including furuncles, would probably have arisen if a more virulent Staphylococcus had been present.

When judged clinically, no response was sufficiently keratotic to justify the term "acneform." No comedones arose and, unlike true acne, the follicular lesions resolved within two weeks after removal of the cups. However, the histologic changes, now to be described, are rather more suggestive of a kinship between this artificial folliculitis and true acne.

No follicular lesions were observed on the control patches of skin covered with sterile salt agar.[1]

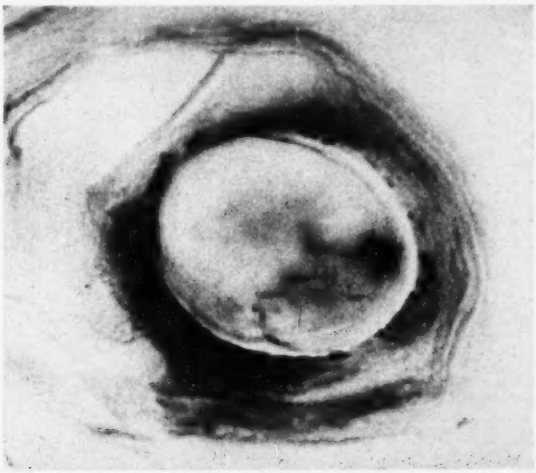

Fig. 1.—Cross section of a normal follicular keratin ring surrounding a hair; from experimentally treated skin, showing apparent staphylococci present in the channel between the ring and the hair; hematoxylin and Biebrich scarlet; × 1,800.

HISTOLOGY

Normal Anatomy of the Mouth of Pilosebaceous Follicle ("Follicular Pore").—The anatomy of the follicular pore, so pertinent to the problem of folliculitis and acne, deserves first consideration.

Like the sweat pore, the follicular opening is surrounded by concentric lamellated keratin disposed in the form of a ring or tube. This structural arrangement, which may be called the follicular keratin ring, is shown in cross section in Figure 1. The keratin encircles the hair and so gives rise to a slit-like channel which, when patent, serves to convey the sebaceous material to the surface.

Figure 2 shows more of these relations in longitudinal section. The ring is seen as a tube-like sheath, the lower edge of which is firmly attached to the inner wall of the neck of the follicle at *A*. Its upper margin is continuous with the stratum corneum of the general integument. The middle and greater portion of the ring is close to the hair, and here, because the section is somewhat tangential, the circular disposition of the keratin is clearly revealed in the form of numerous parallel lines passing across the hair shaft. Figure 1 is a cross section of a follicle at about this level.

The apparent separation of a portion of the keratin ring at *B* from the wall of the follicle produces a space at *C*, external to the ring. This space, which often contains a loose network of keratin squamae, is regarded as an artifact produced by the general shrinkage entailed in paraffin sections. In this regard I have seen no

Fig. 2.—Longitudinal section of the mouth of a normal pilosebaceous follicle, showing relations of the keratin ring. Because of its structure and position the ring probably exerts considerable influence over the escape of sebum; hematoxylin and eosin; × 275.

evidence to suggest that sebum can escape from the follicle through this apparent outer space; moreover, foreign bodies, such as dust particles and bacteria, seem to penetrate only the sebaceous channel between the keratin ring and the hair.

There are obvious anatomic similarities between the follicular keratin ring and the keratin ring present at the sweat pore.[1] A possible functional similarity will be alluded to presently.

Presence of Staphylococci in Follicles.—Figure 1, from these experiments, shows staphylococci in the space between the keratin ring and the hair, that is, in the sebaceous channel. Figure 3 shows this point to better advantage in longitudinal

Fig. 3.—Experimental lesion showing numerous apparent staphylococci in the keratin ring at the neck of a follicle; ring cut longitudinally, the level of the skin surface being indicated by arrows. When stained by Gram stain, bacteria are Gram-positive; hematoxylin and Biebrich scarlet; × 1,200.

section; the sebaceous channel, extending in a line from the top to the bottom of the picture, contains abundant staphylococci. The corresponding hair is just beyond the plane of the section. No rod-shaped bacteria are visible.

The numerous bodies seen in Figures 1 and 3 are presumed to be staphylococci because of their uniform size, shape, and reaction to Gram staining and because in

all experiments no other bacteria could be detected in smears and cultures (aerobic) from the test sites.[4] As previously noted, the observations incriminate staphylococci

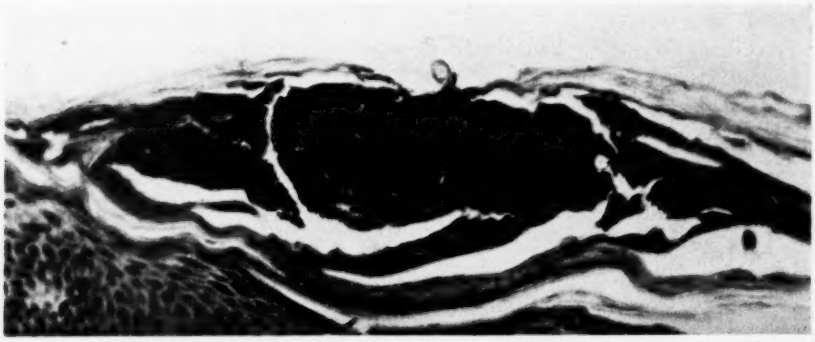

Fig. 4.—Superficial suppurative folliculitis; hair seen at the skin surface; an experimental lesion; hematoxylin and Biebrich scarlet; × 260.

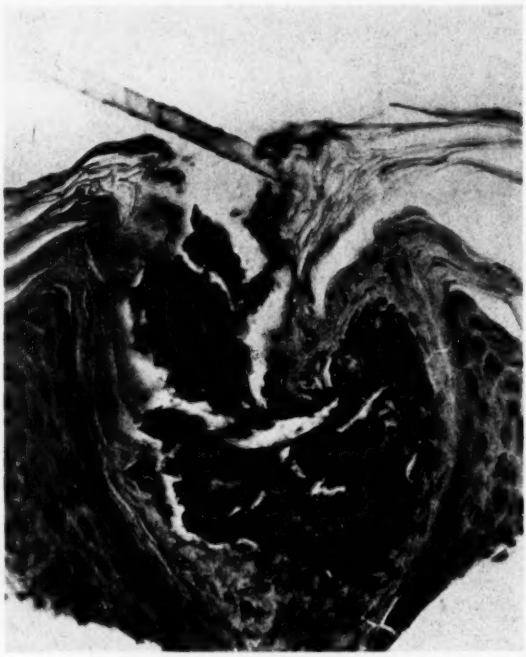

Fig. 5.—Follicular suppuration and surrounding parakeratosis; an experimental lesion; hematoxylin and Biebrich scarlet; × 400.

as a group and not necessarily the particular strain of Staphylococcus applied. Thus, the bacteria in Figures 1 and 3 may have grown from residents of the skin or its follicles.

4. O'Brien,[1] Fig. 22a.

Reaction Produced in the Follicles.—The follicular changes observed on the test side are presumed to have been the result of staphylococcal infection. These changes are illustrated by Figures 4 to 8, in all of which suppuration and parakeratosis are present in varying degree and pattern. Areas of pus appear almost black and generally show artifacts in the form of clefts.

Figure 4 shows early superficial suppurative folliculitis. In Figure 5 the pus cells have congregated deeper in the neck of the follicle, and there is a surrounding early parakeratotic reaction.

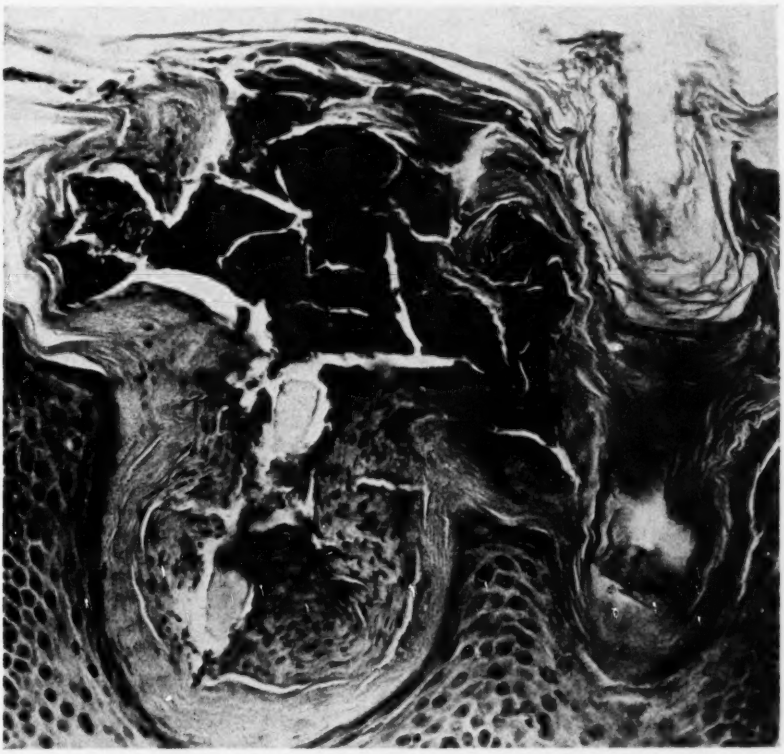

Fig. 6.—Extensive parakeratosis in the neck of a follicle with suppuration closer to the surface; an experimental lesion; hematoxylin and Biebrich scarlet; × 330.

Parakeratosis at the neck of a follicle is predominant in Figure 6. Superficial pus cavities are also present.

The lesion seen in Figures 7 and 8 is of particular interest. Essentially it is a deep follicular pustule associated with a conspicuous parakeratotic plug at the follicular mouth; there is here a strong basic resemblance to the histologic picture of acne vulgaris.

COMMENT

In these experiments, the application of inoculated salt agar to the skin appears to have promoted the growth of staphylococci in the follicles. An inflammatory

response arose which was associated with much parakeratosis. The most important point to be discussed is whether the folliculitis produced in this way has any correspondence with ordinary acne.

Acne and the experimental folliculitis are similar histologically in showing keratosis, obstruction, and infection. Such differences as exist between them are differences in degree rather than in kind; for instance, while keratosis is more prominent in acne, it is still quite a feature in the experimental lesions here described.

Fig. 7.—Parakeratosis at the neck of a follicle with underlying suppuration. The small dark areas indicated by an arrow are masses of cocci in the sebaceous channel. An experimental lesion; hematoxylin and Biebrich scarlet; × 400.

Assuming, therefore, a basic similarity in pattern, it is perhaps not too much to suggest that the keratotic comedo of acne may, likewise, be the result of infection, possibly by staphylococci of relatively low virulence.

This at once raises the old controversy as to whether local infection is "primary" or "secondary" in acne. A full analysis of this matter goes beyond our scope, since the evidence given here is clearly insufficient to dislodge the commonly held modern view that infection in acne is secondary and therefore unessential. Nevertheless, it may be fairly said that, while the proponents of general causes, particularly endocrinal imbalance, have impressive evidence to support their view, the problem is by

no means finally solved. Even if the endocrinal factor is acknowledged as paramount in acne, we are still at a great loss to explain just how it brings about the local lesion. In this regard it is sometimes held, or at least implied, that simple endocrinal stimulation of secretion is responsible, that "hyperactivity," or even mere activity, suffices to produce lesions. Hypotheses of this kind are hardly satisfying. Implicit in them is the idea that the sebaceous apparatus is ill-designed, unstable, or in process of

Fig. 8.—Adjacent serial section of the lesion shown in Figure 7. The appearances are similar to those seen in acne vulgaris; hematoxylin and Biebrich scarlet; × 400.

racial decay. While there may be some truth in these ideas, at least as regards civilized man, it behooves us first to exclude less pessimistic hypotheses.

Several prevalent diseases of the sweat pores have recently been shown to share a common denominator in obstruction ("sweat retention anhidrosis" [5] or "poral

5. Sulzberger, M. B.; Herrmann, F., and Zak, F. G.: Studies of Sweating: I. Preliminary Report with Particular Emphasis on a Sweat Retention Syndrome, J. Invest. Dermat. **9**:221 (Nov.) 1947.

closure" [1]). Our recognition of the importance of obstruction has been of much service because it has directed our attention to underlying causes, and much of value has been achieved. Witness for example the work of Shelley, Horvath, Weidman, and Pillsbury [6] and of Sulzberger,[7] in which many new causes of poral closure have been identified.

The problem of acne may be recast in similar fashion. Although in no way original, the following working hypothesis is proposed.

1. The initial lesion of acne is obstructive in nature.

2. The obstruction is at the follicular keratin ring.

3. Study of the behavior of the follicular ring should prove relevant. On the analogy of the keratin ring at the sweat pore,[1] possible types of reaction to be considered are constriction, swelling (simple edema), infection, and primary hyperkeratosis (parakeratosis).

4. So-called "general causes" of ordinary acne may not act by initiating the essential local obstruction. Rather, by stimulating sebaceous secretion, they make manifest an obstruction produced by local factors, such as have been enumerated in paragraph 3, above.

5. Acne may also resemble miliaria in that "primary" and "secondary" infection cannot be sharply distinguished.

My present supposition is that staphylococcal infection may play a predominant role from the very outset, that without infection acne vulgaris does not occur. This supposition is drawn against the background of much modern work which indicates that a delicate balance is struck between the skin and its staphylococcal flora. The balance is being constantly upset in favor of the invader by general diseases, such as diabetes mellitus, by other skin diseases (leading to true secondary infection), and by environmental factors, such as occur in industry or in the tropics. May not the keratosis and pustulation of acne be just another expression of this never-ending struggle between host and parasite, a sort of long-drawn-out compromise in which neither is truly paramount? Further experiments with the salt-agar technic on patients with actual acne may help to decide the issue and incidentally reveal whether any special strains of staphylococci are associated with the lesions. Goldsmith,[8] using ordinary cultural methods, did not find many staphylococci in acne pustules. However, it is likely that he studied mature lesions.

The interplay of causative factors in acne is possibly more complex than the foregoing hypothesis implies. For instance, general factors (endocrinal or dietetic)

6. Shelley, W. B.; Horvath, P. N.; Weidman, F. D., and Pillsbury, D. M.: Experimental Miliaria in Man: I. Production of Sweat Retention Anidrosis and Vesicles by Means of Iontophoresis, J. Invest. Dermat. **11**:275 (Oct.) 1948. Shelley, W. B., and Horvath, P. N.: Experimental Miliaria in Man: II. Production of Sweat Retention Anidrosis and Miliaria Crystallina by Various Kinds of Injury, ibid. **14**:9 (Jan.) 1950. Shelley, W. B., and Horvath, P. N.: Experimental Miliaria in Man: III. Production of Miliaria Rubra (Prickly Heat), ibid. **14**:193 (March) 1950.

7. Sulzberger and others.[5] Sulzberger, M. B.; Zak, F. G., and Herrmann, F.: Studies of Sweating: II. On the Mechanism of Action of Local Antiperspirants, Arch. Dermat. & Syph. **60**:404 (Sept.) 1949. Sulzberger, M. B.; Herrmann, F.; Keller, R., and Pisha, B. V.: Studies of Sweating: III. Experimental Factors Influencing the Function of the Sweat Ducts, J. Invest. Dermat. **14**:91 (Feb.) 1950.

8. Goldsmith, W. N.: Recent Advances in Dermatology, London, J. & A. Churchill, Ltd., 1936, p. 473.

may exert some direct local action apart from mere secretory stimulation. Indeed, clarification of the relations between local and general factors in acne is our most pressing need.

Barber,[9] who has written extensively on this problem, accepts the local comedo (that is, the keratosis and presumably also the obstruction) as simply and directly due to the action of androgens on the skin. This suggestion does not explain satisfactorily the common inflammatory phenomena. He goes on to suggest that male hormone, if secreted into the follicles, may stimulate the growth of resident staphylococci. This possibility had also occurred to me but, using in vitro methods, I have been unable to demonstrate any such stimulatory effect of testosterone on staphylococcal growth. Perhaps male hormone does not act directly on the follicle, but rather there may exist a sex difference in staphylococcal immunity.

No information is available from my work as to what part, if any, the acne bacillus (Corynebacterium acnei) plays in acne.

SUMMARY

At the mouth of the normal hair follicle is a ring-like condensation of keratin which ensheaths the hair. It is probably of importance in the genesis of acne.

In a series of experiments wherein staphylococci were incubated on the skin in conjunction with a nutrient medium, lesions were produced which showed obstruction, keratosis, and suppuration. Sections of early lesions showed the presence of staphylococci in the space between the hair and its sheath of keratin.

Since acne vulgaris shows a somewhat similar histologic picture, it is suggested that staphylococci may play a larger role in the causation of acne than is at present generally believed.

9. Barber, H. W.: Acne Vulgaris, in MacKenna, R. M. B.: Modern Trends in Dermatology, London, Butterworth & Co., Ltd., 1948, p. 125.

FACIAL GRANULOMA WITH EOSINOPHILIA (GRANULOMA FACIALE)

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FROM THE extensive literature recently published concerning "eosinophilic granuloma of the skin," there seems to have emerged a group of cases in which the disease is distinctive enough clinically, and specific enough histologically to constitute an entity. The condition has been called "facial granuloma with eosinophilia" or "granuloma faciale" by Cobane, Straith, and Pinkus [1] and by Lever and Leeper [2] to differentiate it from lesions found accompanying eosinophilic granuloma of bone, with which it apparently has no connection. It is the purpose of this study further to advance the concept of this entity by describing two cases in addition to the nine already reported in the literature.

REPORT OF CASES

CASE 1.—R. C., a 38-year-old woman, was first seen at Mount Sinai Clinic Sept. 24, 1943. At that time she presented an 0.8-by-0.8-cm. nodule on the right cheek, which had been present for one year. The lesion was sharply circumscribed, elevated, skin-colored, doughy in consistency, and asymptomatic. Biopsy was done Jan. 14, 1944, and the report by the Mount Sinai Hospital pathology department was "granuloma with conspicuous eosinophilia." Six x-ray treatments of 100 r each at weekly intervals had no effect on the lesion. A second biopsy was done May 10, 1944. The report was as follows: "Skin shows striking capillary proliferation with diffuse inflammatory reaction; could fit granuloma or infected angioendothelioma." A third biopsy, Sept. 11, 1944, showed "chronic nonspecific inflammation with conspicuous numbers of eosinophiles. Histology rules out sarcoid or tuberculosis; could be persistent papular urticaria." The patient was presented at a meeting of the New York Academy of Medicine in October, 1945, for diagnosis by Dr. Jack Wolf, and shortly thereafter the lesion was desiccated. A new lesion, 0.5 by 0.5 cm. in size and clinically identical with the first, developed in November, 1945, and a report by Dr. Paul Klemperer of a biopsy done on March 1, 1946, was "nonspecific granuloma with conspicuous eosinophiles." On Feb. 17, 1947, a biopsy was again done, and the lesion was removed. Dr. Charles Sims reported on the biopsy as follows: "Massive infiltration in the corium, composed of small round cells, eosinophiles, and wandering connective-tissue cells; many small vessels show swollen intimal cells." The diagnosis was "eosinophilic granuloma of the skin."

The patient was last seen in December, 1949, and presented atrophic scarring at the sites of removal and no recurrence of lesions.

CASE 2.—M. E., a 55-year-old man, had a history of lesions which first appeared on the face in 1946, while he was in Palestine. The lesions were persistent and did not respond to internal

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1. Cobane, J. H.; Straith, C. L., and Pinkus, H.: Facial Granulomas with Eosinophilia, Arch. Dermat. & Syph. **61**:442 (March) 1950.

2. Lever, W. F., and Leeper, R. W.: Eosinophilic Granuloma of the Skin, Arch. Dermat. & Syph. **62**:85 (July) 1950.

medication, including dried yeast, quinine, and other drugs. The patient was first seen at the Mount Sinai Clinic in November, 1950, and at that time presented several sharply circumscribed, raised, slightly purplish lesions, varying in size from 0.5 by 0.5 cm. to 1.2 by 1.2 cm., on the molar eminences and on the forehead. The lesions were asymptomatic, doughy to the touch and had moderate scaling, suggesting chronic discoid lupus erythematosus, which was the tentative diagnosis proposed before biopsy.

A biopsy was done on a lesion on the forehead and showed normal epidermis with massive infiltrates surrounding the vessels of the upper and mid cutis. These infiltrates were composed of lymphocytes, plasma cells, polymorphonuclear leucocytes, and eosinophiles. The infiltrates had not impinged the basal layer of the epidermis which did not show any liquefaction degeneration. A diagnosis of "facial granuloma with eosinophilia" was made (Fig. 1).

Fig. 1 (Case 2).—Multiple lesions on the right cheek, of two years' duration.

There appears to be good evidence that a clinical entity has been described and substantiated by Lever and Leeper [2] and Cobane, Straith, and Pinkus,[1] in coordinating the reports of Buley,[3] Wigley,[4] Oliver,[5] Lever,[6] and others. Eleven cases have now been reported, including the two cases cited above. It is now possible to describe this disease as to its clinical and histologic pictures.

3. Buley, H. M.: Eosinophil Granuloma of Skin, J. Invest. Dermat. **7**:291, 1946.

4. Wigley, J. E. M.: Case for Diagnosis, Brit. J. Dermat. **57**:68, 1948.

5. Oliver, E. A.; Webster, J. R.; Ginsberg, J. E., and Steinberg, H. S.: Eosinophilic Granuloma of the Skin, Arch. Dermat. & Syph. **60**:701 (Nov.) 1949.

6. Lever, W. F.: Eosinophilic Granuloma of Skin, Arch. Dermat. & Syph. **55**:194 (Feb.) 1947.

CLINICAL PICTURE

The characteristic lesion is a small, asymptomatic nodule or plaque with a regular or irregular sharply circumscribed border. It is soft and elastic to the touch, and varies in color from that of normal skin to reddish brown or purple. The overlying tissue may show exaggeration of the follicular openings and a few small

Fig. 2 (Case 2).—Low-power view of biopsy specimen, showing the normal epidermis, grenz zone of normal cutis, and profuse perivascular infiltrate in the upper and mid cutis.

telangiectases, or there may be a slight scale. These lesions are usually multiple and almost invariably situated on the face or forehead. In one case lesions were found on the shoulder and upper back in addition to the face. The lesions appear to be persistent and in only one case [1] disappeared after "therapy." Eosinophilia of the blood is reported in several cases.

HISTOLOGIC PICTURE

The epidermis is usually normal or flattened, with no liquefaction of the basal layer. Invariably there is a grenz zone of normal cutis directly below the epidermis. The infiltrate, which is usually very pronounced, can be band-like and diffuse throughout the upper and mid cutis, but more often it is perivascular.

Lever and his associates [7] divide the infiltrative changes into two stages: an early leucocytic stage and a late fibrotic stage. In the early stage there is a diffuse

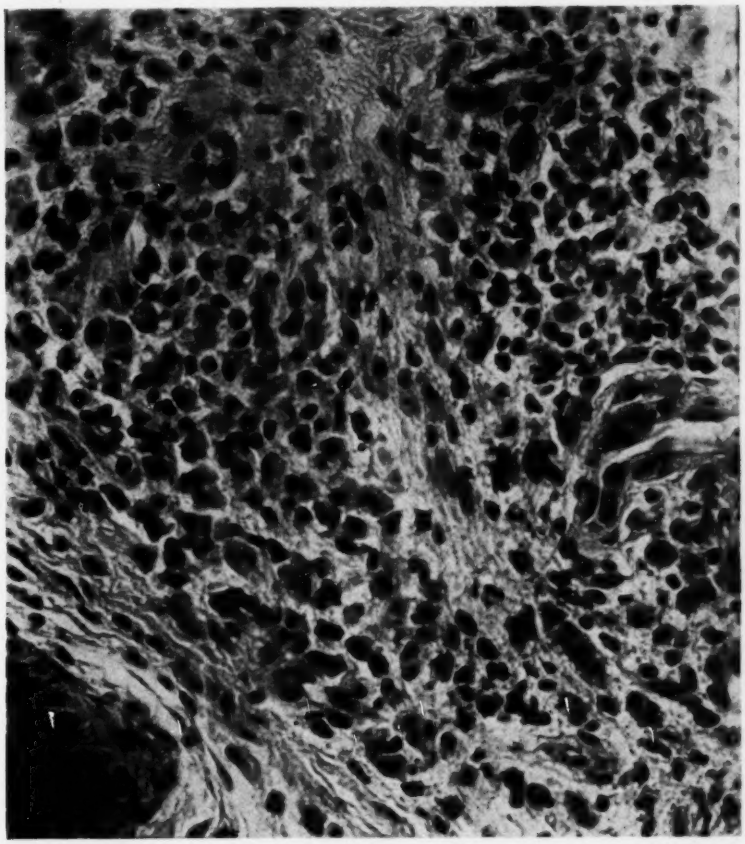

Fig. 3 (Case 2).—High-power view, demonstrating the polymorphous nature of the infiltrate, including eosinophiles, plasma cells, polymorphonuclear leucocytes, and histiocytes.

infiltrate, densest around the capillaries, composed of eosinophiles, neutrophiles, and histiocytes, with eosinophiles predominating. The capillaries are dilated, with swelling of the endothelial cells, and there may be extravasation of red cells with hemosiderin. A dense network of fine reticulum fibers permeates the infiltrate. In the later stages there is a polymorphism of cell types in the infiltrate, with a decrease

7. Lever, W. F.; Lane, C. G.; Downing, J. G., and Spangler, A. S.: Eosinophilic Granuloma of Skin: Report of 3 Cases, Arch. Dermat. & Syph. **58**:430 (Oct.) 1948.

in eosinophiles and neutrophiles and an increase in lymphocytes, plasma cells, and fibroblasts. The vessels show thickening, with fibrosis of the walls. In one case foam cells were seen.

Cobane, Straith, and Pinkus point out, "characteristic changes of the perivascular tissue, resembling fibrinoid degeneration or toxic hyalin, but not necessarily identical

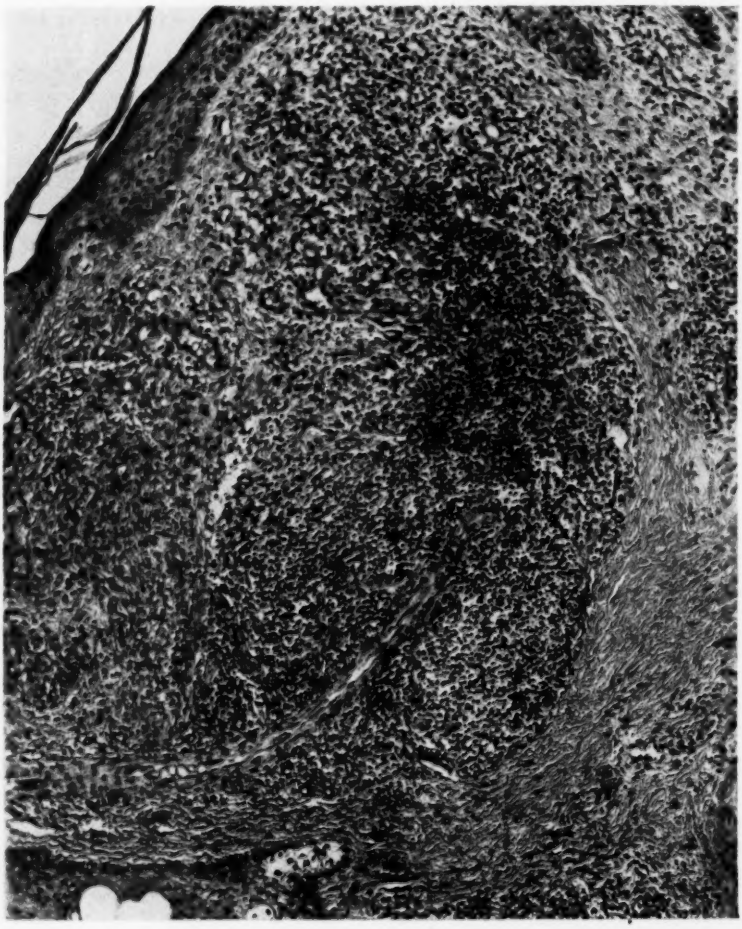

Fig. 4 (Case 1).—Low-power view of early lesion, demonstrating the profuse perivascular infiltrate in the upper, mid, and deep cutis. The epidermis is normal, and there is a small grenz zone of normal cutis.

with it, accentuate the impression that the blood vessels are the centers of the pathologic process."

These histologic changes are evident in the biopsy specimens of the two patients whose cases are herein reported. Figures 2, 3, and 4 demonstrate the early stage in this disease. The epidermis is normal, the basal layer intact. There is a zone

of normal cutis directly beneath the basal layer. There is a marked infiltrate, perivascular in distribution, in the upper and mid cutis. This infiltrate is composed of eosinophiles, neutrophiles, plasma cells, lymphocytes, and histiocytes. The vascular changes are not yet prominent in this stage. Case 1 offers a better opportunity to study the pathogenesis of this disease, in that biopsy specimens of the lesions at all

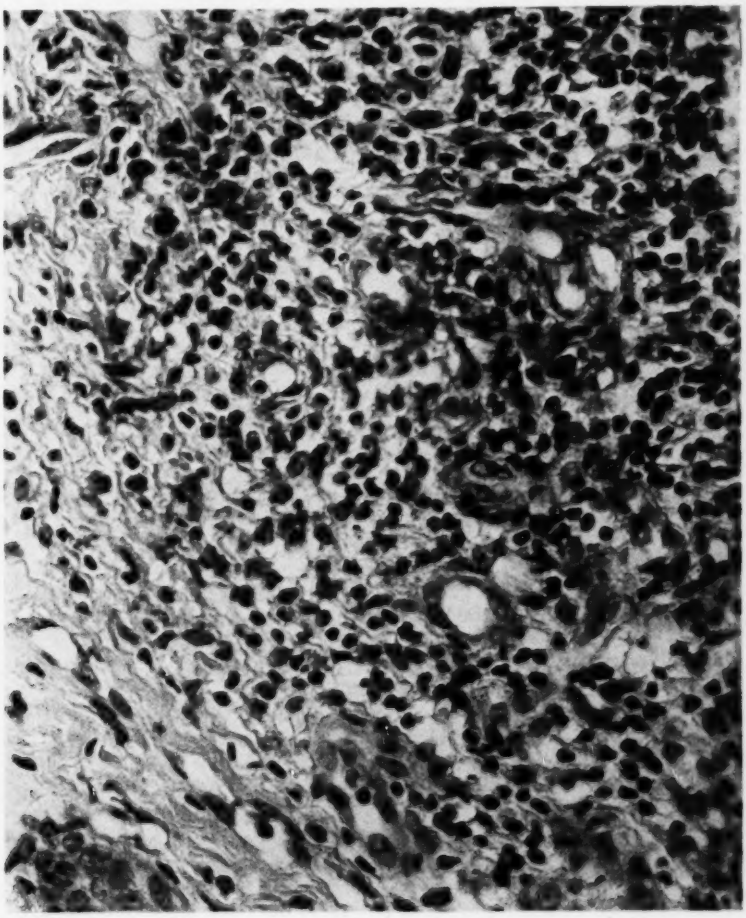

Fig. 5 (Case 1).—High-power view of infiltrate in early lesion, demonstrating the eosinophilic nature of the infiltrate.

stages were obtained. Figures 4 and 5 again demonstrate the typical early changes. Figure 6 shows a beginning fibrosis with more uniformity of the infiltrate; the eosinophiles and neutrophiles are less prominent, and fibroblasts are becoming more evident. There is marked endothelial thickening and "fibrinoid" changes in the vessels are evident. Many of the vessels are completely occluded.

DIFFERENTIAL DIAGNOSIS

Erythema Perstans.—The lesions of erythema perstans may be raised and sharply circumscribed but are usually erythematous and pruritic. They show intermittent exacerbations and remissions and have a different histologic picture.

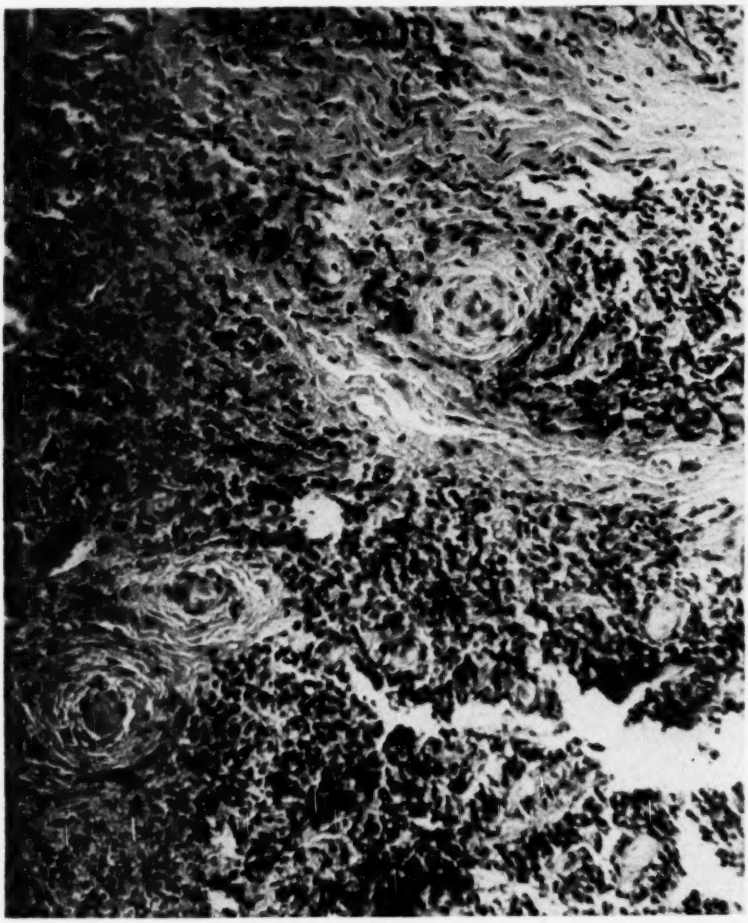

Fig. 6 (Case 1).—High-power view of later lesion, demonstrating the increase in fibrosis and marked thickening and proliferation of the vessels in the lower cutis.

Granuloma Annulare.—Although the typical lesion of granuloma annulare is usually gyrate with raised erythematous borders, it may occur in nodular form. It is differentiated from granuloma faciale by its therapeutic response to x-rays, and by histologic section.

Discoid Lupus Erythematosus.—When typical, this disease offers no diagnostic difficulty. However, in the deep type described by Irgang, infiltrated plaques may be a prominent feature. Here again biopsy will easily differentiate the two diseases.

Lymphocytoma.—Lesions of lymphocytoma, although usually deeper and more indurated than facial granuloma, occasionally resemble the latter (Loveman and Fliegelman,[8] Mopper and Rogin[9]). These extremely rare lesions are radiosensitive and can be differentiated histologically.

Leukemia Cutis.—The lesions are usually multiple, grow rapidly, and are often accompanied with typical blood and bone marrow changes. The histology is typical and can be differentiated from facial granuloma.

Erythema Elevatum Diutinum.—The lesions of erythema elevatum diutinum very rarely involve the face, are much firmer to the touch, and show a tendency to coalesce not seen in facial granuloma. Histologically the epidermis is acanthotic, and there is a perivasculitis consisting of many polymorphonuclear leucocytes with few, if any, eosinophiles.

Sarcoid Lesions.—These are usually multiple, infiltrated nodules or plaques, with accompanying systemic manifestations and a characteristic histological picture.

Leprosy.—The lepromatous form of leprosy may in the early stages consist of isolated nodules on the face. Here again laboratory procedures, including biopsy, should determine the diagnosis.

Mycosis Fungoides.—Nodular lesions very rarely precede the typical premycotic manifestations of mycosis fungoides. The d'emblée type is a fast-growing, ulcerating lesion which should not be too difficult to differentiate from the indolent asymptomatic lesion of facial granuloma.

Syphilis.—Erythematous, sharply circumscribed lesions on the face can be seen in secondary syphilis. Biopsy and a positive serologic reaction readily differentiate this disease from granuloma faciale.

Drug Eruption.—Occasionally drug sensitivity causes isolated erythematous patches on the face. Clinically the lesions are more superficial, of a more transitory nature, and present a different histologic picture from that of facial granuloma.

SUMMARY

1. The concept of a new entity, facial granuloma with eosinophilia as first described by Cobane, Straith, and Pinkus and by Lever and Leeper, is further substantiated by the presentation of two additional cases.

2. This disease is characterized clinically by single or multiple, sharply circumscribed, raised, soft, skin-to-purplish-colored nodular lesions. These lesions are almost completely confined to the face and are asymptomatic and resistant to therapy, including x-rays. Histologically, the early lesion shows a massive band-like or perivascular infiltrate in the upper and mid cutis, with a preponderance of eosinophiles. Later there is fibrosis, with a lessening in the number of eosinophiles, and a gradual proliferation, with intimal and "fibrinoid" changes in the vessels of the upper and mid cutis.

33 E. 70th St. (21)

870 Fifth Ave. (21)

35 E. 84th St. (21)

8. Loveman, A. B., and Fliegelman, M. T.: Lymphocytoma Cutis: Report of 2 Cases, A. M. A. Arch. Dermat. & Syph. **63**:169 (Feb.) 1951.

9. Mopper, C., and Rogin, J. R.: Benign Solitary Lymphocytoma: Report of 3 Cases, A. M. A. Arch. Dermat. & Syph. **63**:184 (Feb.) 1951.

EFFECT OF AN ORAL EMULSIFYING AGENT ON SERUM LIPIDS IN PATIENTS WITH CHRONIC DERMATOSES

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EMULSIFYING agents administered orally are stated to improve the absorption of fat [1] and fat-soluble vitamins [2] from the gastrointestinal tract. Marked improvement of a secondary pellagra-like eruption was observed in a patient with idiopathic steatorrhea treated in this manner. This response suggested the possibility that faulty fat absorption may produce abnormalities in skin metabolism; the thick, dry, hyperpigmented skin in biliary cirrhosis and intestinal lipodystrophy are cases in point.[3]

Alterations of the composition of tissue fat have been observed in rats fed a fat-deficient diet,[4] and small doses of the C-18 unsaturated fatty acids have caused healing of the desquamated epithelial surfaces caused by this deficiency.[5] In patients with eczematous dermatitis the low iodine numbers of the serum fatty acids were increased by the feeding of unsaturated fatty acids, and there was concomitant improvement in the skin.[6] In psoriatic patients the surface fat from the uninvolved skin has been reported to have a lower-than-normal acid and iodine number and a significantly lower estercholesterol quotient.[7] Vitamin E has been demonstrated in the surface fat of skin and in the sebum of man recently.[8] Beneficial effects have

This study was supported by a grant from the Abbott Research Laboratories.

From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School (Dr. Marion B. Sulzberger, Chairman) and the Skin and Cancer Unit of New York University Hospital.

1. May, C. D., and Lowe, C. W.: The Absorption of Orally Administered Emulsified Lipid in Normal Children and in Children with Steatorrhea, J. Clin. Invest. **27**:226 (March) 1948.

2. Sobel, A. E.; Sherman, M.; Lichtblau, J.; Snow, S., and Kramer, B.: Comparison of Vitamin A Liver Storage Following Administration of Vitamin A in Oily and Aqueous Media, J. Nutrition **35**:325 (Feb.) 1948.

3. Ahrens, E. H., Jr.; Payne, M. A.; Kunkel, H. G.; Eisenmenger, W. J., and Blondheim, S. H.: Primary Biliary Cirrhosis, Medicine **29**:299 (Dec.) 1950.

4. Barnes, R. H.; Miller, E. S., and Barr, G. O.: Fat Absorption in Essential Fatty Acid Deficiency, J. Biol. Chem. **140**:773 (Sept.) 1941.

5. Calvery, H. O.; Draize, J. H., and Lang, E. P.: Metabolism and Permeability of Normal Skin, Physiol. Rev. **26**:495 (Oct.) 1946.

6. Hansen, A. E.; Knott, E. M.; Wiese, H.; Shaperman, E., and McQuarrie, I.: Eczema and Essential Fatty Acids, Am. J. Dis. Child. **73**:1 (Jan.) 1947. Stoesser, A. V.: Influence of Soybean Products on the Iodine Number and Plasma Lipids and the Cause of Eczema, J. Allergy **18**:29 (Jan.) 1947.

7. Rothman, S.: Arch. Dermat. & Syph., to be published.

8. MacKenna, R. M. B.: The Composition of Surface Skin Fat (Sebum) from the Human Forearm, J. Invest. Dermat. **15**:33 (July) 1950.

been reported in patients with various chronic dermatoses following the administration of fat-soluble vitamins.[9]

It is the purpose of this paper to report observations upon 85 dermatologic patients treated with an orally administered detergent, with special emphasis on the results of laboratory studies of the serum lipids. Sorethytan (20) monooleate, commonly known as "tween 80," was used in this investigation. Studies of the levels of the serum lipids in nine of these patients are given in detail as they appear to be of considerable interest, especially since we have been unable to find any reports in the literature of the effects of oral administration of sorethytan (20) monooleate on the serum lipids in man. Reports of the effects of orally administered sorethytan (20) monooleate in man have heretofore dealt with fat absorption as measured by stool fat content and vitamin-A absorption.

METHODS

Eighty-five patients were studied, 37 men and 48 women. One half of these had atopic dermatitis, 25 had psoriasis and the remainder had various dermatoses. Approximately one-half were over 45 years old. The great majority of these patients had been receiving topical therapy and antihistaminic drugs orally before being given sorethytan (20) monooleate. Since previous therapy was continued unchanged, each patient served as his own control. Six grams of sorethytan (20) monooleate orally per day was prescribed for all patients. Eighty ambulatory patients were given the drug in the form of "sorlate"[10] in 0.5 gm. capsules (4 capsules three times daily with meals) for varied lengths of time, ranging from two weeks to three months. They were instructed to eat a "moderate fat" diet, which in most cases was their usual diet. Five hospitalized patients were given the drug in undiluted liquid form (1.5 gm. with breakfast and supper, and 3 gm. with dinner) for varying periods. They were offered a diet containing 100 gm. of fat (0.46 to 0.78 gm. cholesterol), 120 gm. of protein, and 270 gm. of carbohydrate (a total of 2,650 calories) per day which was taken well except by two patients (Cases 2 and 8). Levels of serum lipid were measured by the following methods: total lipids by the Bloor method,[11] total and esterified cholesterol by the procedure of Bloor and Knudson,[12] and lipid phosphorus by the procedure of Whitehorn.[13] Fatty acids were calculated according to the formulas of Bloor.[11] Total phospholipids were expressed in terms of lecithin (lipid P $\times$ 25).

RESULTS

The clinical impression was that the administration of sorethytan (20) monooleate orally was beneficial in certain dermatoses. Softening of the dry, rough,

9. Frazier, C. W., and Hu, C. K.: Cutaneous Lesions Associated with Deficiency of Vitamin A, Arch. Int. Med. **48**:507 (Sept.) 1931. Burgess, J. F.: Vitamin E (Tocopherols) in Collagenoses, Lancet **2**:715 (Aug.) 1948.

10. "Sorlate" was supplied by Dr. A. E. Osterberg, Abbott Research Laboratories.

11. Bloor, W. R.: The Determination of Small Amounts of Lipid in Blood Plasma, J. Biol. Chem. **77**:53 (April) 1928.

12. Bloor, W. R., and Knudson, A.: The Separate Determination of Cholesterol and Cholesterol Esters in Small Amounts of Blood, J. Biol. Chem. **27**:107 (Oct.) 1916; Cholesterol and its Esters in Blood, ibid. **29**:7 (Feb.) 1917.

13. Whitehorn, J. C.: A Method for the Determination of Lipoid Phosphorus in Blood and Plasma, J. Biol. Chem. **62**:133 (Nov.) 1924.

lichenified skin was noted in some chronic dermatoses, such as atopic dermatitis, psoriasis, and allergic eczematous contact-type dermatitis. Similarly, the dryness of senile and ichthyotic skins was sometimes noted to become less. Since other therapy was given concomitantly, and since these chronic diseases often undergo natural remissions, the present series should be extended and be more rigidly controlled before one can venture more than the clinical impression given at this time.

Fasting Serum Lipid Levels Before and After Oral Therapy with Sorethytan (20) Monooleate

Case No.	Age, Yr.	Sex	Duration of Therapy, Days		Total Lipids, Mg. per 100 Ml.	Fatty Acids, Mg. per 100 Ml.	Phospho-lipids, Mg. per 100 Ml.	Choles-terol, Mg. per 100 Ml.	Choles-terol Esters, Mg. per 100 Ml.	Ester: Total* Choles-terol	Choles-terol: Phospho-lipid*
Normal					500-700	200-420	175-350	160-230	100-150	40-60	< 1
A. Psoriasis											
1†	60	M	12	Before	780	573	187	215	...	..	1.15
				After	914	647	310	270	...	..	.87
				% Change	+17	+13	+68	+26	...	..	....
2†	62	M	15	Before	618	462	237	185	...	..	.78
				After	713	502	230	215	...	..	.93
				% Change	+15	+9	−2	+16	...	..	....
3	22	F	15	Before	540	...	...	135	65	48	....
				After	1,148	1,107	225	165	85	51	.73
				% Change	+113	...	...	+22	+31	+6	....
4†	48	F	48	Before	547	361	270	185	...	..	.69
				After	836	686	282	180	105	58	.64
				% Change	+53	+90	+6	−3	...	..	....
B. Atopic dermatitis											
5	40	F	86	Before	405	271	247	195	...	..	.79
				After	979	703	325	280	...	..	.86
				% Change	+141	+159	+33	+44	...	..	....
6	48	M	54	Before	976	686	345	345	...	..	1.00
				After	1,103	726	...	375	...	..	....
				% Change	+13	+7	...	+9	...	..	....
C. Distinctive exudative discoid and lichenoid chronic dermatosis											
7†	64	M	26	Before	510	536	237	160	...	..	.68
				After	908	663	317	250	...	..	.79
				% Change	+78	+24	+34	+56	...	..	....
D. Acquired epidermolysis bullosa											
8†	32	M	12	Before	450	...	...	135	65	48	....
				After	570	303	225	180	105	58	.80
				% Change	+27	...	...	+33	+62	+21	....
E. Ichthyosiform erythrodermic nevus											
9	41	M	30	Before	615	416	162	150	85	56	.93
				After	578	381	250	195	105	53	.78
				% Change	−6	−8	+56	+22	+24	−5	....
	46	N	33	Before	611	472	223	189	71	51	.86
				After	861	615	286	234	98	54	.77
	Average			% Change	+41	+31	+27	+24	...	..	−9

* Ratio on basis of weight.
† Hospitalized during study.

Diarrhea was not a common complaint, but many patients who had taken laxatives for years found that they were no longer necessary, as reported previously by Jones and his associates.[14] Five patients complained of distention with some flatus, and two of an undesirable gain in weight. An 84-year-old patient, who had had three severe attacks of coronary thrombosis, had a relatively mild attack while on this medication. No evidence of toxicity has been reported in patients receiving 15 gm. of sorethytan (20) monooleate daily by mouth over a period of many months.[14]

14. Jones, C. M.; Culver, P. J.; Drummey, G. D., and Ryan, A. E.: Modification of Fat Absorption in the Digestive Tract by the Use of an Emulsifying Agent, Ann. Int. Med. **29**:1 (July) 1948.

Levels of serum lipids were determined before and after therapy in nine patients (Table). The stated normal values for serum lipids by the present methods have been determined in the Biochemical Laboratory of the New York Post-Graduate Hospital, now known as the University Hospital, by Mattice in extensive series of normal subjects.[15]

Total lipids were increased in eight out of nine patients. There was an average percentage increase of 41% for total lipids, 31% for fatty acids, 27% for phospholipids, and 24% for cholesterol. It will be noted that the changes in the lipid fractions are not large, and in some cases may reflect normal day-to-day variations. However, in five patients the level of total lipids after therapy rose to 900 mg. per 100 ml. or higher, which is distinctly in the abnormal range. In the face of these changes, the cholesterol : phospholipid ratio did not shift significantly.

COMMENT

Kellner and his associates [16] have produced arteriosclerosis in rabbits with great regularity by feeding sorethytan (20) monooleate orally with a high cholesterol diet. Under this regimen and in this species the cholesterol : phospholipid ratio rose to extremely high levels, in distinction to the present series. However, the possibility of similarly increasing serum cholesterol levels and producing arteriosclerosis in man suggests that the protracted oral administration of sorethytan (20) monooleate should be handled with caution. The failure of the cholesterol : phospholipid ratio to increase in the present series of patients may be due to species variation, lower cholesterol intake, or shorter duration of oral administration of sorethytan (20) monooleate. It is not known whether this enhancement of serum lipids while on oral therapy with sorethytan (20) monooleate is due to enhanced absorption of exogenous fat or to other mechanisms, for example, increased lipid synthesis in the tissues of such organs as the liver and the skin.

SUMMARY

1. An emulsifying agent, sorethytan (20) monooleate ("tween 80"), was administered orally to 85 patients with chronic dermatoses.

2. In certain instances "softening" of the skin was noted to follow the use of this agent, but this preliminary clinical impression requires confirmation by a more rigidly controlled series of patients.

3. Levels of serum lipids rose in eight of nine patients, in five patients exceeding 900 mg. per 100 ml. There was no significant change in the cholesterol : phospholipid ratio.

1538 Sherbrooke St., W. (25).

15. Mattice, M. R.: Chemical Procedures for Clinical Laboratories, Philadelphia, Lea & Febiger, 1936.

16. Kellner, A.; Correll, J. W., and Ladd, A. T.: Modification of Experimental Atherosclerosis by Means of Intravenous Detergents, Am. Heart J. **38**:460 (Sept.) 1949.

Clinical Notes

SELENIUM DISULFIDE SUSPENSION IN TREATMENT OF SEBORRHEIC DERMATITIS OF THE SCALP

ALBERT H. SLEPYAN, M.D.
HIGHLAND PARK, ILL.

The treatment of seborrheic dermatitis of the scalp at times plagues both patient and practitioner. There are many patients who remain free of the underlying erythema, scaling, and itching only as long as they are faithful and persistent in the use of ointments, lotions, and shampoos at daily, semiweekly, or weekly intervals. This can become a time-consuming problem, as well as a source of annoyance to the patient and those who live within the immediate orbit of these repetitive treatments, not only because of the frequent application, but because of the disagreeable odors of tars and sulfurs, not to mention the soiling of linens and furniture.

The purpose of this communication is to report the results of a clinical trial of a medicament containing selenium disulfide [1] in the treatment of seborrheic dermatitis of the scalp. Selenium, because of its relative closeness to sulfur in the periodic table, has long been suspected of having properties similar to sulfur. In the search for newer and more efficient substances in the treatment of seborrheic dermatitis, selenium disulfide was hypothesized to be effective therapeutically. Because of the many unfavorable toxicological reports involving selenium, the Kettering Laboratories undertook studies on animals, and later on humans, relative to the absorption of selenium following the use of this medicament.[2] Slinger and Hubbard [3] repeated these studies and followed with an excellent pharmacological and clinical report on a suspension of selenium disulfide in the treatment of seborrheic dermatitis of the scalp. These preliminary observations indicated that the preparation could be used without risk under appropriate conditions. There was no sign of cutaneous irritation or sensitivity in the group studies, and absorption and excretion studies revealed the substance to be safe for general use.

PROCEDURE

In this study the seborrheic dermatitides of the scalp of 286 patients were classified as follows: (1) pityriasis sicca, a dry branny type of desquamation, either in small patches or involving the entire scalp; (2) pityriasis steatoides, an oily type of dandruff often associated with erythema, greasy crusting, and itching; (3) psoriasiform seborrhea, as manifested by oily crusting and a tendency to configurate patches, and (4) seborrhea oleosa, characterized by exceedingly oily hair, often matted and lifeless, in which the patient usually gives a history of having to wash the scalp two or three times a week and occasionally complains of an offensive odor.

After the patients were classified, each was given a bottle of the suspension of selenium disulfide ("selsun") and a typewritten slip containing the following instructions for the use of the shampoo:

1. Wet head thoroughly with warm water either before or after regular washing procedures.
2. Apply 1 to 2 teaspoons (4 to 10 ml.) of selenium disulfide suspension and work into scalp until lather is obtained.
3. Rinse and repeat process.

From the Department of Dermatology and Syphilology, University of Illinois (Francis E. Senear, M.D., Chairman).

1. Selenium disulfide suspension was supplied by Dr. Arnold Osterberg of the Abbott Laboratories, under the trade name of "selsun."

2. Kehoe, R., and Goldman, L.: Communication to Abbott Laboratories.

3. Slinger, W. N., and Hubbard, D. N.: Treatment of Seborrheic Dermatitis with a Shampoo Containing Selenium Disulfide, A. M. A. Arch. Dermat. & Syph. **64**:41 (July) 1951.

4. Allow a lather of the preparation to remain in contact with scalp for a total of approximately five minutes.
5. Rinse scalp thoroughly by using changes of water or by showering.

The suspension of selenium disulfide used had the following approximate composition:

Selenium disulfide	2.5
A surface-active agent naccenol® (NRSF)	17.0
Inert and stabilizing ingredients	5.2
Water, sufficient to make	100.0

RESULTS

Improvement was most marked in the group classified as pityriasis sicca. Seventy-six patients, or 92%, were cleared after two to four weeks (Table). Pityriasis steatoides was the largest group observed. Of these patients, 204, or 85.7%, were cleared. A good number of these have been using the medicament routinely for over six months. The two patients observed with seborrhea oleosa were not improved. Both felt that their hair became oilier after treatment and refused further treatment after several washings. The four patients with psoriasiform seborrhea were helped only partially; the addition of a classic sulfur and salicylic acid cream with the suspension of selenium disulfide brought about clearing. Itchings here was controlled with the use of the preparation alone.

Of those patients recorded as showing no improvement, 20 with pityriasis steatoides discontinued treatment after several weeks because of increased oiliness of the hair. It is noteworthy

Results of Therapeutic Use of Selenium Disulfide Suspension in Seborrheic Dermatitis of the Scalp Observed Over an Eight-Month Period

Classification	Patients, No.	Cleared		Improved But Not Cleared		No Improvement	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
1. Pityriasis sicca	76	70	92.2	2	2.6	4	5.2
2. Pityriasis steatoides	204	180	85.7	4	4.6	20	9.8
3. Psoriasiform seborrhea	4	0	0	4	100	0	0
4. Seborrhea oleosa	2	0	0	0	0	2	100
Total	286	250	87	10	3.8	26	9.2

that those who complained of itching prior to use of the medicament were free of itching when they discontinued treatment because of the increased oiliness. Four patients objected to the alkaline odor of the preparation. Two patients refused to continue with the treatment because of an orange tint imparted to their gray hair. However, several patients with gray hair continued to use the shampoo, followed by a rinse to overcome the orange tint.

It was interesting to note the improvement in the scalps of 59 patients with acne vulgaris and acne juvenilis. Nine patients with atopic eczema were greatly benefited. Five patients with psoriasis were watched. The selenium disulfide preparation alone was incapable of clearing the scalp. However, when it was used in conjunction with ammoniated mercury and salicylic acid ointments, clearing was obtained.

SUMMARY AND CONCLUSIONS

In a series of 286 patients, selenium disulfide suspension ("selsun") alone was capable of controlling seborrheic dermatitis of the scalp in 87% of all cases. Simple dandruff or pityriasis sicca responded in 92% of cases, whereas pityriasis steatoides was controlled in 85% of the group studied. Psoriasiform seborrhea was improved but not cleared without additional local therapy. Itching in seborrhea oleosa was controlled, but the oiliness of the hair was exaggerated.

Scalps of patients with acne vulgaris, acne juvenilis, and atopic eczema were benefited.

There was no sign of intoxication, sensitization, or irritation noted over an eight-month period.

So simple a method of treating seborrheic dermatitis of the scalp makes selenium disulfide suspension an important addition to dermatologic therapeutics.

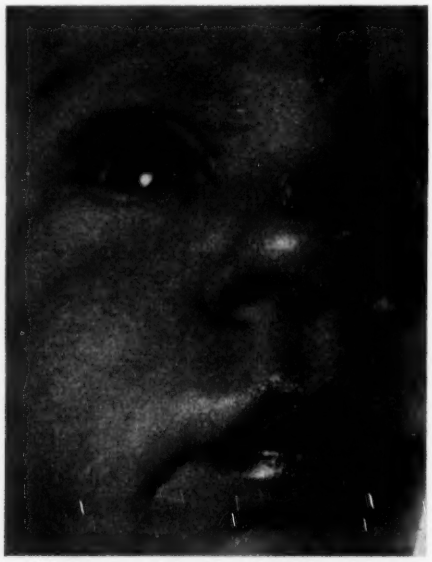
2 N. Sheridan Rd.

PRENATAL WART

F. RONCHESE, M.D.
PROVIDENCE, R. I.

Ordinarily the appearance of a wart on the nose of a 19-week-old baby would suggest merely an unusual location of a common lesion at an unusual age and would present a certain degree of therapeutic problem. The chief concern of the physician in such a case ordinarily would have to do with the method of removal with a minimum of trauma and scarring.

In the present case, however, the extraordinary feature consisted of the statements of the pediatrician, Dr. F. Giunta, and the obstetrician, Dr. A. L. Potter, that at birth there was present a round elevation, about 1.5 mm. in height and about 3 mm. in width, in the exact location of the wart.



Common digitate wart on the nose of a 19-week-old baby, which apparently developed from warty lesions present at birth.

These observations were corroborated by the child's father, a college professor, who stated that he saw the infant 20 minutes after birth and noted three small elevations of the dimensions mentioned above and in the same location.

The pediatrician noted that when the child was 6 weeks old the tumor had become more elevated but was still round and without projections.

At 12 weeks, the tumor had become even larger, but digitations were not present. When digitations first appeared, they were thought to consist of caseous material extruding from a cyst.

The parents deny having noted any warts on themselves or on relatives or friends who may have handled the baby.

In view of these circumstances, it is apparent that the wart developed in utero.

In his extensive survey of the literature on skin disease of the fetus, Lynch [1] mentions one case of fibroma and one of xanthoma present at birth. In the long list of prenatal diseases affecting the skin of the fetus, warts are not mentioned.

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1. Lynch, F. W.: Dermatologic Conditions of the Fetus with Particular Reference to Variola and Vaccinia, Arch. Dermat. & Syph. **26**:997 (Dec.) 1932.

SUMMARY

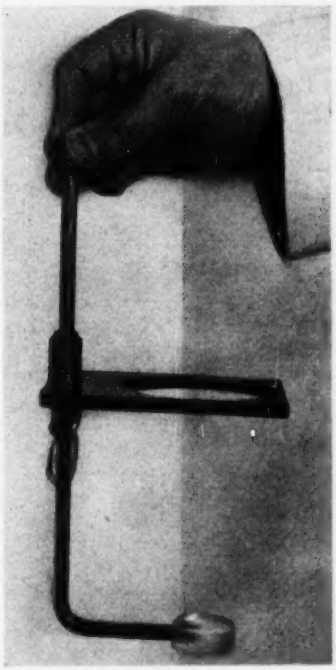
A case is reported of a common digitate wart on the nose of a 19-week-old baby girl which, according to the obstetrician, pediatrician, and parents, was present at birth.

170 Waterman St.

MEASURING AND CENTERING DEVICE FOR USE ON X-RAY MACHINE

MILTON S. ROSS, M.D.
MOUNT KISCO, N. Y.

The accompanying picture is of a device to be used on the tube head of the profexray® low-voltage therapy x-ray apparatus. It is intended as a simplified device for centering the x-ray beam and measuring the focus-skin distance.



Measuring and centering device especially adapted for use on the profexray® low-voltage therapy x-ray apparatus.

As may be noted in the picture, the filter carrier is employed to hold the centering and measuring rod. The filter carrier is a nonconductive material, such as plastic. It fits snugly in a slot provided for it in the tube head. With the filter carrier in place, the lucite® disk, about the size of a quarter in diameter, is in the center of the x-ray beam. The measuring rod, bent at its lower end at an angle of 90 degrees, is inserted into the side of the disk so that the rod tip is seen at the exact center. The rod slips easily up and down through its supporting post in the filter carrier. The rod may also be turned easily so that the disk may pass through a complete circle. A spring clip is attached as shown or may be inserted inside the post so that the motion of the rod in all directions is controlled. When the rod is adjusted, it is held in place by the

clip. The rod, made of brass, aluminum, or other suitable metal, is flat at its external surface—the disk is set in the beam center as shown. The flat surface provides an area for calibrations principally of 15 cm., 20 cm., 25 cm., and 30 cm. and also provides a surface by which the spring or spring clip holds the rod in place.

The device is operated as follows: The filter-carrier portion is inserted into the slot in the tube head provided. A click indicates that it is completely in and that a device permitting operation with a filter is operating. The lucite® disk is swung into the center of the x-ray beam directly under the x-ray tube portal and rests there with the clip pressed against the flat surface of the rod. The rod is now moved up or down to the desired height. The tube head is then manipulated so that the lucite® disk touches the center of the lesion. The portion of the lesion, small or large, may be visualized through the lucite disk. This is especially helpful if the lesion is small. The tube head is locked in place. The disk is then easily swung away, out of the beam. It may be lifted up first and then swung away, or it may be swung away, left there, or then pushed up. Treatment may then be given accurately.

359 E. Main St.

CROSSED FIXED DRUG ERUPTION FROM TWO ANTIBIOTICS

ASHTON L. WELSH, M.D.
CINCINNATI

I have experienced a fixed drug eruption from aureomycin.[1] Terramycin was ingested on two occasions between the periods of ingestion of aureomycin and preceding the fixed eruption produced by the latter drug. No eruption or untoward reaction of any type occurred from ingestion of terramycin on these occasions.

After the eruption appeared from aureomycin, taken for the last episode of upper respiratory infection for which it was used,[1] terramycin was administered to complete treatment. The lesions of the fixed eruption from aureomycin became more marked and persisted much longer than the earlier episodes of eruption, in the same sites produced by aureomycin alone. At that time, this increase in severity and prolonged interval of the fixed drug eruption from aureomycin were not attributed to terramycin. The phenomena were interpreted as having their basis in increased sensitization to aureomycin due to repeated ingestion of this drug.

Six months later, terramycin (one dose of 500 mg.) was again taken for another attack of upper respiratory infection. Pruritus was experienced within two hours on all of the sites of former eruption from aureomycin. These sites were easily recognized by the persistent pigmentation. In four hours, erythema appeared at each site of the fixed eruption from aureomycin. In two more hours (six hours after ingestion) urticaria and bullae appeared at several of the same sites. There was no eruption elsewhere. Pruritus, however, became generalized. Only one dose of terramycin was ingested.

The pruritus subsided in two days, and the eruption faded in about five days. The pigmentation at each site of the fixed eruption from aureomycin became more pronounced after the reaction to terramycin.

This same series of events occurred a second time, after one 250-mg. dose of terramycin was taken to determine positively that this drug was actually capable of producing the crossed fixed drug eruption described above.

No other instance of crossed fixed drug eruption from the antibiotics was found. The observation recorded above suggests some common sensitizing factor in aureomycin and terramycin.

1219 Carew Tower.

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1. Welsh, A. L., and Goldberg, L. C.: Fixed Drug Eruption from Aureomycin: Report of 2 Cases, A. M. A. Arch. Dermat. & Syph. **64**:356 (Sept.) 1951.

PROMACETIN® THERAPY OF DERMATITIS HERPETIFORMIS

LEON GOLDMAN, M.D.
CINCINNATI

Sulfoxone sodium (diasone®) has been used by Cornbleet [1] since 1944 in the treatment of dermatitis herpetiformis. He has indicated that he has obtained good results. A much less toxic sulfone, also used in the treatment of leprosy, has been under study in the Department of Dermatology at the University of Cincinnati College of Medicine since 1949. This preparation is an acetosulfone (promacetin®) (sodium 4,4'-diaminodiphenylsulfone-2-acetylsulfonamide) for the treatment of sarcoidosis. The toxic reactions seen during this period of study have included only occasional nausea, one probable drug-allergy reaction of pharyngitis, and one drug fever. No serious blood or renal disturbances have been seen, even on prolonged courses. It appears, then, that promacetin® may be used when treatment must be continued for some time.

After Cornbleet's report, promacetin® was used in the treatment of nine patients with dermatitis herpetiformis with an average initial dose each of 0.5 gm. four times a day for several weeks and then reduction to 1 gm. with an average maintenance dose of 1.0 to 0.5 daily. In two cases 3 gm. daily was used. In general the response to promacetin® seemed less rapid than to sulfapyridine. In one patient a severe flare-up occurred during promacetin® therapy. Three patients have had equally rapid responses, however. Six patients with so-called nummular dermatitis of the hands have also been treated, with temporary initially good responses. It is hoped that wider experience with this drug will reveal the dosage schedule to be followed. Because of the maintenance of blood levels following even single doses, it may be possible to use schedules of only single doses.

Maintenance regimens have been held up to six months now without any evident toxic reactions. However, one must always be alert for such reactions since this material is a sulfone, although much less toxic than others.

441 Vine St. (2)

Promacetin® was obtained from Eugene H. Payne, M.D., Parke, Davis & Company, Detroit.

From the Department of Dermatology and Syphilology, University of Cincinnati College of Medicine.

1. Cornbleet, T. A.: Personal communication to the author.

HEMANGIOMA WITH SCLEROSIS

Report of a Case

JULIUS E. GINSBERG, M.D.
CHICAGO
AND
DONALD P. MUSGRAVE, M.D.
FULLERTON, CALIF.

Sclerosis in old hemangiomas is not infrequently observed by histopathologists, but such cases are rather seldom reported. They sometimes offer an interesting problem in differential diagnosis, and hence we present this report.

P. G., a 68-year-old white man, was first seen by us in January, 1951, at which time he was treated for a mild seborrhoea capitis. During the physical examination a firm reddish-brown plaque was observed on the lateral aspect of the right ankle. The lesion was symptomless. It was approximately 0.75 cm. wide and 1.5 cm. long. There was no inguinal lymphadenopathy, and there were no similar lesions elsewhere on the body.

From the Department of Dermatology, Northwestern University Medical School, Herbert Rattner, M.D., Chairman.

Fig. 1.—Firm reddish-brown small plaque; crust showing biopsy site.

Fig. 2.—Low-power photomicrograph showing sclerosing islands of vascular tissue disseminated in the dermis, and subepidermal hemosiderosis and sclerosis.

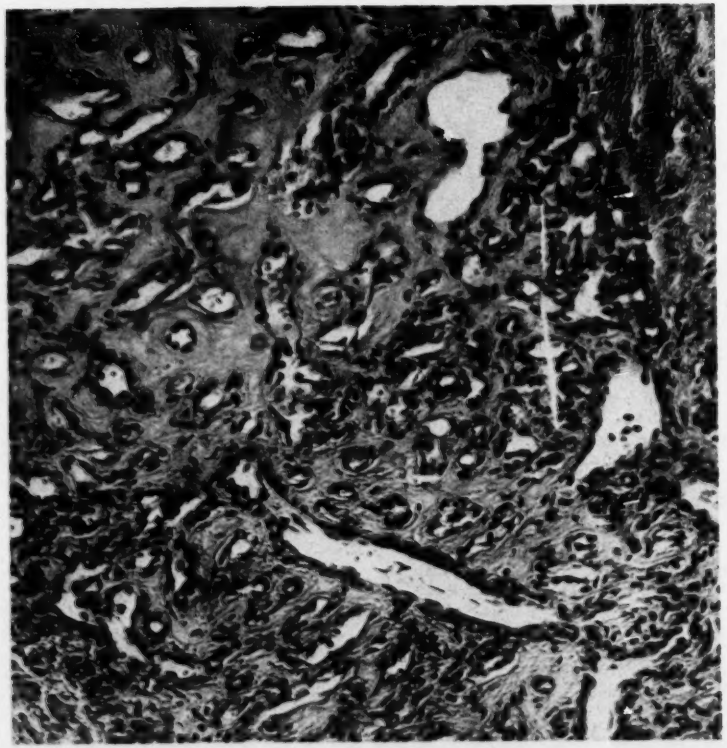

Fig. 3.—Detail magnification of island of hemangioma showing collagen formation and sclerosis about the vessels and obliteration of some of the blood vessels in this process.

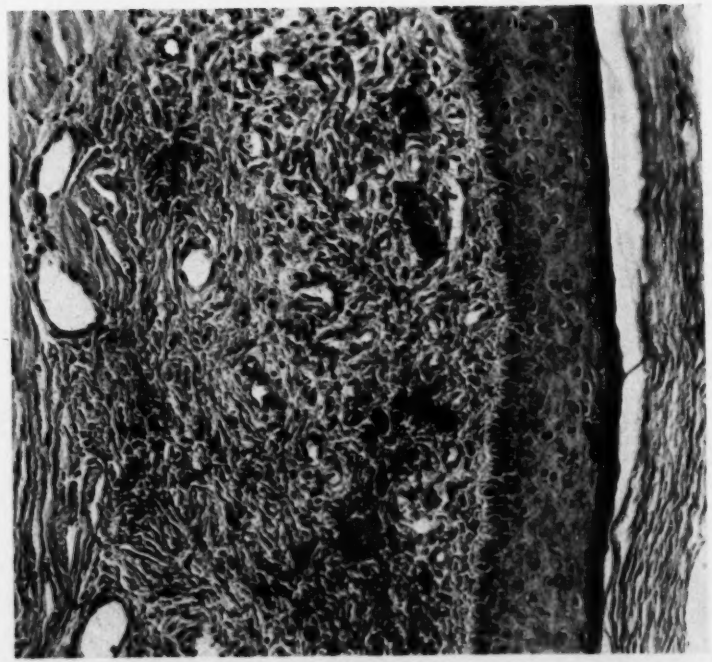

Fig. 4.—Detail magnification of superficial portion of tumor showing hemosiderosis (proved by iron stain), sclerosis, and partial obliteration of vascular element by this process of fibrosis.

The patient had first noted the lesion when he was 28 years old, but he could not recall very much about possible changes in appearance during the 40 years of its existence, nor could he recall a definite preceding and possibly associated trauma.

The general physical examination otherwise and laboratory findings were in keeping with his age.

A punch biopsy was performed, and the clinical and microscopic pictures are shown here.

COMMENT

Multiple idiopathic hemorrhagic sarcoma of Kaposi was considered clinically, but it is quite likely that other lesions would have appeared during the 40 years if this condition were present. Histologically the growth resembles somewhat the sclerosing stage of this disease.

The gross and microscopic features, particularly those seen in the superficial dermis, resemble a great deal those described by Gross and Wolbach for sclerosing hemangiomas.[1]

Ancient granuloma pyogenicum with sclerosis is both a clinical and a histologic possibility.

The chance is small that the lesion represents a simple hypertrophic hemangioma with subsequent sclerosis, because of its first appearance at the age of 28.

Hemangioendothelioma and malignant melanoma are easily ruled out on the basis of the histologic findings.

The diagnosis as given is simply a morphologic one.

826 E. 61st St.

109 N. Malden St.

1. Gross, R. E., and Wolbach, S. B.: Sclerosing Hemangiomas, Am. J. Path. **19**:533 (July) 1943.

LIVER-FUNCTION TESTS IN STASIS DERMATITIS

PAUL R. GRIFFITH, M.D.
AND
CARL F. BAUMEISTER, M.D.
BERWYN, ILL.

It has been felt by numerous observers that malfunction of the liver plays a definite role in certain skin diseases. Stasis dermatitis has received the attention in this respect of several qualified authors, but most of them have been dermatologists. Since we felt that research into the relationship of liver disease and stasis dermatitis was a rather broad subject to be covered by one specialty, we decided to join our efforts on the problem.

Stasis dermatitis is a chronic, subacute, or even acute, eczematoid dermatitis involving the lower legs and ankles. It is often accompanied by edema and sometimes by ulcers of the involved areas, and it is thought to result from an impairment of either or both the blood and the lymph circulation of the extremity. In most cases stasis dermatitis is due to varicose veins, and the condition clears when the veins have been treated adequately.[1] However, there are not infrequently patients with stasis-type dermatitis who have no demonstrable varices and no signs of lymph stasis and others who have a recurrence of the dermatitis after the previous varicosities have been treated as efficaciously as possible.[2]

From the Departments of Dermatology and Internal Medicine, University of Illinois College of Medicine.

1. Wolf, M.: Cutaneous and Subcutaneous Lesions of the Lower Limbs in Connection with the Veins, J. Am. Dermat. Soc. **52**:376, 1945. Naide, M.: Allergic Lesions Following Thrombophlebitis, Arch. Int. Med. **80**:388-396 (Sept.) 1947. Smith, F.: Diagnosis and Treatment of Conditions Associated with Varicose Veins, Minnesota Med. **24**:175, 1941.

2. Callaway, J. L.; Riley, K. A.; Kuhn, B. H., and Barefoot, S. W.: Dermatitis Hypostatica: Combined Dermatological and Surgical Treatment, South. M. J. **39**:375-382, 1946.

As has been pointed out by previous authors, sometimes stasis dermatitis is cured by treatment of concomitant tinea of the feet or by removal of some focus of infection quite distant from the leg, such as carious teeth or infected tonsils. However, because a certain number of these cases remain quite inexplicable, it was felt that an attempt to discover a relationship between malfunctions of the liver and stasis dermatitis might prove fruitful.

METHOD OF STUDY

The cases of stasis dermatitis were found and the condition diagnosed in the department of dermatology, and the patients were then referred to the department of medicine for study.

A complete history was obtained, physical examination was performed, and a thorough search was made for all types of disease, but particularly those involving the hepatic and cardiovascular systems. For each patient a complete blood count, urinalysis, electrocardiogram and chest roentgenogram were made, as a minimum.

The liver-function tests were chosen to give as good a comparative "liver profile" as possible.[3] These tests covered the following functions of the liver: excretion, detoxification, and metabolism of carbohydrates, proteins, and fats.

REPORT OF CASES

Dermatologic findings in our series of cases of stasis dermatitis were as follows:

CASE 394-264.—A 54-year-old woman presented erythematous papular dermatitis with excoriations and eroded vesicles. There was moderate edema of both lower legs, and small superficial varices on the thighs, but no large ones.

CASE 353-555.—A 42-year-old woman presented varicose ulcer in the medial aspect of the distal third of the right leg. There was severe eczematoid dermatitis on the rest of the right lower leg, some on the left lower leg, and moderate edema on the right lower leg. Moderately large varices were present. Ligation was done Jan. 1, 1950, and the dermatitis was very much better Feb. 1, 1950.

CASE 279-663.—A 62-year-old man had varicose ulcer on the right ankle with edema and erythematous and scaly dermatitis on the right ankle and lower leg. There was a history of old thrombophlebitis following herniotomy in 1933.

CASE 330-407.—A 61-year-old man presented eczematoid dermatitis on the lateral aspect of the right ankle, with numerous small ulcers, edema, and marked varicosities of the right leg. Deep thrombophlebitis was present.

CASE 351-756.—A 63-year-old woman had a patch of red scaly eczema 3½ in. (9 cm.) in diameter on the medial aspect of the right ankle, with an ulcer ¾ in. (2 cm.) in diameter in the center of it. There were many varices.

CASE 353-259.—A 56-year-old woman presented three ulcers on the right lower leg, with extensive eruption surrounding the ulcers. There was much edema of the right lower leg.

The clinical findings of the department of medicine and the results of the liver-function tests are presented in the Table.

COMMENT

In our series of cases it is at once apparent that there was no consistent laboratory evidence of liver damage. This is at considerable variance with the results obtained by certain other investigators.[4]

Relationship of Other Diseases.—Studies by others have not been complete with regard to the general physical condition of the patient and other diseases from which he might be suffering. In five of our six patients arteriosclerotic heart disease was found. It was in an early stage in

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3. Brick, I. B.: Laboratory Aids in Evaluating Status of Liver, Am. Pract. **3**:732-735, 1949. Lockwood, B. C.: Tests for Hepatic Function and Disease, Harper Hosp. Bull. **6**:91-99, 1948. King, E. J.: Liver Function Tests, Irish J. M. Sc. **282**:245-260, 1949. Butt, H. R.: Present Day Status of Tests of Hepatic Function, J. Indiana M. A. **42**:120-125, 1949.

4. (*a*) Footnote 1. (*b*) Callaway.[2] (*c*) Eichenlaub, F. J., and Osbourn, R. A.: Role of the Liver in Congestive Eczema, Arch. Dermat. & Syph. **57**:171-175 (Feb.) 1948.

Summary of Clinical Data and Results of Liver-Function Tests on Patients with Stasis Dermatitis

Case Number	Sex	Age	Liver Size	Other Clinical Findings of Interest for Diagnosis	Sulfobromophthalein Sodium U. S. P. 5 to 8%- 30 Min. 0-45 Min.	A/G Ratio; 5.5 Gm. Total; Ratio 1.7/1	Exton-Rose 3d Spec. 175 Top	Icteric Index, 6-8	Cholesterol, 250 Mg.	Remarks
294-264	F	54	Not enlarged	1. Arteriosclerotic heart disease, grade 1; moderate enlargement left ventricle 2. Mild hormocytic anemia 3. Mild diabetes mellitus	30-5% 45-0	8.3 total; 6.3/2; 3:1	86, 182, 178	6	288	.....
353-555	F	42	Not enlarged	1. Cholecystitis	30-10% 45-8%	8.3 total; 5.4/2.9; 1.8:1	79, 16, 131	6	267	Cholecystitis and (+) sulfobromophthalein sodium test
279-663	M	62	Down 1 cm. and tender	1. Arteriosclerotic heart disease, grade 2; widened aorta with pulmonary congestion; pulmonary fibrosis and emphysema 2. Removal of carcinoma of rectum 7 yr. before	30-2% 45-0	6.7 total; 4.3/2.4; 1.8:1	79, 182, 163	6	462	.....
330-407	M	61	Not enlarged	1. Ulcerative colitis with iron-deficiency anemia 2. Arteriosclerotic heart disease, grade 1	30-8% 45-0	7.3 total; 4.6/2.7; 1.8:1	79, 133, 133	4	177	.....
351-756	F	63	Not enlarged	1. Nonvisualizing gall bladder 2. Hypertensive cardiovascular disease, grade 1	30-11.5% 45-4%	6.9 total; 4.6/2.3; 2:1	83, 154, 136	5	185	Cholecystitis and (+) sulfobromophthalein sodium test
353-259	F	56	Down 1 cm. and tender	1. Hypertensive cardiovascular disease, grade 2 to 3	30-5% 45-0	7.7 total; 5.1/2.6; 2:1	95, 194, 222	7	195	.....

three but moderately advanced in the remainder. A conclusion as to whether it is a factor in the production of stasis dermatitis is beyond the scope of this paper.

Further than this, in some cases there were factors which might well have been productive of positive livre function tests. In two patients gall bladder disease [5] was found, and in one, ulcerative colitis.

Similar Functions Possessed Jointly by the Skin and Liver.—The point has been advanced that the liver and skin possess jointly so many similar functions that a disturbance of one organ must surely be reflected in the other in many instances. The functions commonly felt to be possessed jointly are metabolism or storage of carbohydrate and cholesterol, and synthesis of vitamins and pigments. However, the liver makes vitamin A and the skin makes vitamin D. The pigments made by the liver are the bile pigments, very little of which is, to our knowledge, produced by the skin. As to metabolism of carbohydrate and cholesterol, there is no convincing evidence that the skin has any important or clear-cut role in this matter.

Liver Function Tests in This Study.—As far as a careful search of the literature reveals,[6] our liver profile studies are as thorough as those done by any of the workers on this particular type of problem. However, the liver has many complex functions.[7] Since a good many of these functions involve problems of intermediary metabolism,[8] vitamins, etc., they are not very well understood. The liver has a great deal of reserve capacity, and it is recognized that only a fraction of the organ may carry on its necessary work. All of these considerations must be borne in mind when one attempts to test its functions.[9]

Our Rejection of the Theses.—After seeing results like those presented here, one is able to understand why Ketron [10] has assumed a skeptical attitude toward the fruitfulness of internal surveys or of special studies of certain organs in the approach to most dermatological problems. However, we do not have such a cynical feeling, but rather believe that frank and careful research may be of immeasurable value.

If there should be a relationship between deranged liver function and stasis dermatitis, then it seems logical that in cases in which the clinical diagnosis of severe liver disease is apparent there should also be some stasis dermatitis. One of us (P. R. G.) was dermatologist for the 12th General Hospital in the Mediterranean Theater for 34 months during World War II. In this hospital there were over 2,000 patients with acute infectious hepatitis, many of them with severe disease and there was not a single case of stasis dermatitis.

CONCLUSION

No consistent relationship between the role of the liver and stasis dermatitis could be established by our studies.

6820 Windsor Ave.

6804 Windsor Ave.

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Society Transactions

MANHATTAN DERMATOLOGIC SOCIETY

Paul E. Bechet, M.D., *Co-President*

Isadore Rosen, M.D., *Co-President*

George M. Lewis, M.D., *Secretary*

Jan. 9, 1951

Scleroderma; Sclerodermatomyositis. Presented by Dr. George C. Andrews.

J. D., a Jugoslavian woman aged 39, noted some brown spots the size of a quarter on the inner surface of the left hip in 1934. These gradually increased in size. Later, similar spots appeared on the interior aspect of the left arm. In 1937 the patient married and subsequently gave birth to three healthy children. During pregnancy, spots began to appear more extensively, and other parts of the body, especially on the left side, became involved. In 1943 the fingers of the left hand became numb and twitched, and contractures developed. Shortly afterward, twitchings with paresthesia developed on the other arm and both legs. In 1944 she began to have pain in the joints of the left hand and leg, and the numbness spread.

The left upper extremity is in its entirety thinner and weaker than the right. The medial surface of the upper part of the left arm is hyperpigmented, with irregular marmoreal spots. Similar hyperpigmented and apigmented places are found also on the interior surface of the left hip, on the thigh, and in the hypogastric area. The skin of the upper and lower part of the arm is fixed and cannot be elevated in folds. The muscles of the left shoulder and arm are particularly atrophic; the circumference of the upper part of the arm is 24 cm., while the corresponding part of the right arm is 26 cm. There is also a difference of 2 to 3 cm. above the elbow joint and below it. All the fingers except the thumb are flexed and ankylosed. The skin on the dorsum of the right hand is atrophic and bright, and below it is atrophy of the metacarpal musculature. There is partial ankylosis of both elbow joints, which cannot extend or flex in an angle larger than 135 degrees. The group of ulnar flexor muscles of the right arm are also atrophic. The interphalangeal joints of the arms and legs are somewhat blown up and less movable. Interosseal muscles of the left arm are atrophic. The difference in the thickness of the lower extremities is between 3 and 5 cm.

The report of biopsies was as follows: Sections of a large piece of voluntary-muscle tissue disclosed both focal and diffuse infiltrations of mononuclear cells, evidently lymphocytes. Some of the focal infiltrations were rather large and in these locations one saw evidence of degeneration of the muscle fibers. These fibers might be frayed or showed a basophilic reaction. In some instances there was a loss of the transverse striae. Some of these infiltrations appeared to be in the muscle tissue proper, but others were in the interstitial connective tissue. In the center of one such infiltrate there were large cells which suggested a reticuloendothelial origin. Small round cells were seen in strand-like infiltrations between numerous voluntary muscle fibers. The diagnosis was myositis.

Sections of skin disclosed epidermis which had undergone parakeratosis in the neighborhood of an infundibulum. Most of the epidermis appeared to be somewhat thinned. Parts of it were hyperpigmented. The cutis showed evidence of a chronic inflamatory reaction, which was focal, perivascular, and perifollicular. The infiltrating cells were mononuclear and small and resembled lymphocytes. There was no evidence of sclerodermatous change, although a few fibers were, perhaps, somewhat hyalinized. Most of the connective-tissue bundles were thin. The very thin fibers showed evidence of basophilic degeneration, in other words, the formation of elacin. The diagnosis was dermatitis (Dr. G. F. Machacek).

DISCUSSION

Dr. Samuel M. Peck: I have seen and published the peculiar case of a patient in whom dermatomyositis was followed by progressive atrophy but not scleroderma, and was confined to one half of the body (*Dermat. Ztschr.* **52**:82, 1938). A number of years later I saw a patient

of Dr. Wise's in whom again the dermatomyositis was followed by atrophy instead of scleroderma, also confined practically to one half of the body.

DR. MAURICE J. COSTELLO: Was there any history of injury? Not long ago I saw a patient in whom a similar condition developed after injury.

DR. GEORGE C. ANDREWS: This condition followed childbirth.

DR. ANTHONY N. DOMONKOS (by invitation). She had a complete examination, including electroencephalograms, and there were no changes.

Secondary Syphilis. Presented by DR. NATHAN SOBEL.

S. G., a man aged 37, is presented from the New York Skin and Cancer Hospital. He was treated at a clinic in 1936 for early latent syphilis. He had had a penile sore three months earlier. The Wassermann reaction was 4+ in 1936. He was treated with 34 injections of arsphenamine and 55 injections of bismuth. Spinal-fluid examinations in 1938 and 1939 showed normal findings. The serologic reactions became negative in 1939 and remained so until 1941. In 1946 he again had a penile lesion and was seen by his physician, who gave him injections of penicillin. When seen again at the clinic his serologic reactions were positive, as follows:

	Kolmer	Venereal Disease Research Laboratories Test
Sept. 16, 1948	4+	1:10
March 28, 1949	4+	1:10
Oct. 19, 1949	4+	1:2
Nov. 28, 1949	4+	1:2
June 10, 1950	4+	1:20
Oct. 10, 1950	4+	1:40

At the New York Skin and Cancer Hospital on Jan. 5, 1951, the patient stated that he had had a skin condition, of three months' duration, on the palms. Examination showed several desquamated areas on the palms and soles, small lichenoid papules on the glans penis, and two silver-dollar-sized, infiltrated, red areas on the scrotum. Dark field examination of a scrotal lesion showed Treponema pallidum.

DISCUSSION

DR. DAVID BLOOM: I saw this patient a few days ago, and, in spite of the positive serologic reaction, the lesion on the glans penis impressed me as psoriasis. It appears to be considerably improved following a few injection of penicillin. Of course, this therapeutic result, together with the positive findings from dark field examination and the moist papules around the anus, force us to accept it as secondary syphilis.

DR. ISADORE ROSEN: I am sorry I did not see this patient before he received antisyphilitic therapy. Seeing him tonight for the first time I did not think of psoriasis but of lichen planus because of the unusual purple color and the small papules on the penis. The lesions on the palms and on the scrotum suggest the type of syphilis met with in the late secondary period. This patient probably had an anal chancre four or five months ago.

Spiegler-Fendt Sarcoid. Presented by DR. PAUL GROSS.

Arsenical Melanosis; Multiple Infected Sebaceous Cysts; Epitheliomas. Presented by DR. GEORGE C. ANDREWS.

Paul E. Bechet, M.D., *Co-President*

Isadore Rosen, M.D., *Co-President*

George M. Lewis, M.D., *Secretary*

Feb. 13, 1951

Bullous Dermatosis Associated with Hyperglobulinemia, Proteinuria, and Plasmocytosis of the Bone Marrow; Drug Sensitivity Reaction(?). Presented by DR. ORLANDO CANIZARES.

The patient, a man aged 55, was hospitalized for 48 hours in July, 1950, with abdominal cramps associated with diarrhea and nausea. Findings from blood studies were essentially normal. The patient was told he had some protein in the urine which was probably due to a kidney infection. He was instructed to take gantrisin® (a sulfonamide compound), 0.5 gm. three

times a day, starting July 9, 1950, and he did so until Sept. 5. Within 48 hours after starting treatment the patient noticed bullae on the dorsa of the feet. There was an increasing number of bullae on the buttocks, scrotum, hands, and feet. He was treated locally only until Sept. 5, when he was hospitalized for thorough study, which revealed albuminuria, elevated serum globulin, and plasmocytosis of the bone marrow. The diagnosis of multiple myeloma was made, and on a skin biopsy the diagnosis was pemphigus. The patient was treated with a course of corticotropin (ACTH), 520 mg. in 13 days, with no change in the course of the illness. He was then transferred to the Bronx Veterans' Administration Hospital on Nov. 14.

The skin lesions are nonpruritic, and the patient has pain only when the bullae become tense. There has been no appreciable weight loss and no bone pain.

The patient states that for the past several years he has been having routine physical examinations and has been told that everything is all right. The last examination was in December, 1949. Pneumonia developed in January, 1950, and he was treated at home for three weeks with penicillin in sesame oil, sulfamerazine, and sulfadiazine, one tablet of each every three to four hours around the clock.

Because of the possibility of a sulfonamide reaction, the patient was given a test dose of succinylsulfathiazole (sulfasuxidine®), and within 24 hours there was a new crop of bullae. New bullae continued to develop almost daily, especially on the dorsa of the feet and hands and occasionally in the bearded area where he shaves. He has continued on an ambulatory basis, and except for the bullae he has no complaints.

Results of physical examination are essentially normal except for bullae on the dorsa of the right foot and the hands. There are a few denuded areas on the hands. Xanthelasma and torus palatinus are present.

Hemograms were normal. Urinalysis showed albuminuria (4+) with granular and hyaline casts. Bence Jones protein was absent. Globulin was present in the urine. Blood-urea clearance was 100% in the first specimen and 88% in the second. The urea nitrogen was 17 mg. per 100 cc. Uroporphyrin studies disclosed no abnormality. A Congo red test showed 74% of the dye retained in the serum at the end of 45 minutes. The total cholesterol was 236 per 100 cc. The Venereal Disease Research Laboratory reaction for syphilis was negative.

The total protein varied, on three examinations, from 7.2 to 7.6 gm. Albumin varied from 2.6 gm., and globulin, from 4.8 to 5.2 gm. Electrophoresis revealed elevation of the alpha globulin and gamma globulin. Beta globulin was normal. Sulfonamide-level determinations revealed 0.2 mg. on Dec. 7, 1950, none on Dec. 21, and 0.25 mg. on Jan. 26. The bone marrow showed a plasmocyte count of 38.5% and a plasmoblast count of 5%, a total of 43.5%.

Report of the biopsy of the skin was either epidermolysis bullosa or pemphigus.

Roentgenograms of the bones and chest were normal, and an intravenous pyelogram was likewise normal.

DISCUSSION

DR. WILBERT SACHS: The section shows two types of lesions, one subepidermal and one intraepidermal. There is no cellular reaction associated with either, certainly not the polymorphonuclear leucocytes and eosinophils that one finds in pemphigus. I do not think it is epidermolysis bullosa, although if it were just subepidermic I would consider that. The intraepidermic reaction is not of the same type as in chronic benign familial pemphigus. I think it is more a toxic type of bullous lesion, possibly associated with a neoplasm. It is not unlike one that Dr. Cipollaro showed. I have never seen such a bullous lesion from sulfonamide drugs. I do not think it is pemphigus, but there is a toxic bullous lesion, and I would say possibly coincident with a neoplasm, probably of the abdomen.

DR. DAVID BLOOM: This case confirms again my repeatedly expressed theory that there are some instances of epidermolyses bullosa produced by sulfonamides. Such a case was presented by me at this society in October, 1949, namely, the case of a nurse who was sensitized to sulfonamides by external applications and in whom an eruption resembling pemphigus vulgaris developed, and later an eruption which could not be distinguished from the severe dystrophic type of epidermolysis bullosa developed. That case was presented by me here and reported in the *New York State Journal of Medicine* (**43**:1499 [Aug. 15] 1943). That drugs could produce irreversible skin damage leading to an eruption which resembles a hereditary skin disease should not be surprising.

DR. PAUL GROSS: There seems to be a contradiction in what has been said. I can readily understand the toxic effect from the sulfonamide drug resulting in a prolonged skin eruption. This is made very doubtful by the statement that new bullae appeared after a single dose of succinylsulfathiazole. Such a reaction would have to be looked upon as allergic.

DR. SAMUEL M. PECK: I have also seen epidermolysis-bullosa-like eruptions in patients with multiple myeloma. However, as far as this case is concerned, the eruption elicited by drugs is often conditioned by the basic response of the shock tissue. If we were to have a patient with a borderline purpura hemorrhagica and if a drug were to affect the bone marrow particularly, then the toxic manifestations following the drug would be a purpura. In this instance, owing to a tendency to bullae because of multiple myeloma, it is not inconceivable that the precipitation of a bullous eruption by a drug is an indirect one by some effect on the bone marrow. In such cases, skin reactions would be negative.

DR. ANTHONY C. CIPOLLARO: I thought this was a simple case of dermatitis medicamentosa proved by the reappearance of lesions after the suspected drug was given.

DR. SAMUEL M. PECK: It is possible with all the systemic damage this patient shows, that any drug might cause such a reaction.

DR. PAUL GROSS: It is well known that iododerma can be fatal in patients who have kidney disease, because of the retention.

DR. DAVID BLOOM: The kidney damage, together with the skin damage, may very well have been produced in this patient by the sulfonamide drugs.

DR. ORLANDO CANIZARES: The patient had pneumonia six months before the abdominal pain and received sulfonamide drugs. No urinalysis, blood count, or other laboratory work was done, as he was treated at home. When we first saw the patient we made a diagnosis of epidermolysis bullosa, but when we started asking questions we became more hesitant. Does he have a reaction to sulfonamide drugs, including kidney damage? Does he have multiple myeloma? All three possibilities can be argued very well. Dr. Peck's explanation of the reaction should be taken very seriously. Possibly the patient does not have multiple myeloma, mainly because of the globulins, whose pattern is not that of multiple myeloma, but good hematologists still think he has. The internists are rather gloomy about him. They think there has been permanent damage to the kidneys.

A Case for Diagnosis: Erythema Annulare Centrifugum? Presented by DR. DAVID BLOOM.
Pseudoxanthoma Elasticum; Angioid Streaks of the Retina. Presented by DR. JOCK WOLF.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Paul Gross, M.D., *Chairman*

Anthony C. Cipollaro, M.D., *Secretary*

Jan. 2, 1951

Pemphigus Vulgaris Preceded by Pemphigus Erythematosus. Presented by DR. JESSE A. TOLMACH.

C. M., a Jewish woman aged 68, born in Russia, is presented from Beth Israel Hospital. About three years ago she noticed red, scaly spots on the face, scalp, armpits, and chest. The eruption was persistent and slightly itchy. She consulted her family physician and went to various clinics, where she was told that the eruption might be psoriasis. An ointment and some liquid medicine were prescribed, which she took on and off without appreciable improvement.

When she first visited Beth Israel clinic on Nov. 2, 1949, the eruption had been present for about two years. It then consisted of hyperkeratotic, crusted, erythematous patches involving the armpits, nose, chest, and abdomen. Removal of the crusts revealed a granulating, bleeding base, and the picture assumed the character of rupioid psoriasis. In March, 1950, the eruption underwent a sudden change; the former erythematous scaly lesions presented pinhead- to hazel-nut-sized bullae with clear contents, rupturing on pressure and exposing a bright-red, moist surface. The lesions were predominantly in the genital and lumbar regions and appeared for the first time also in the oral and nasal cavities. There was considerable itching, especially at the onset of a new outbreak. The patient's general health was unaffected, the only complaints being anorexia and insomnia.

The results of urinalysis were normal, serologic reactions for syphilis were negative, and the blood count was as follows: 4,140,000 red cells, and 7,100 white cells, with 48% polymorphonuclear leucocytes, 2% staff cells, 42% lymphocytes, 4% monocytes, and 4% eosinophils.

When the patient was first seen, a tentative diagnosis of psoriasis was made, considering the possibility of pemphigus of the Senear-Usher type. Treatment first consisted of liver injection, ultraviolet irradiation, and, later, sulfonamides and aureomycin. The response was poor, and when cortisone became available, she was admitted to the hospital on July 18. During the first 10 days, 1.5 gm. of cortisone was given, with dramatic response. The lesions involuted completely, leaving brownish, pigmented, smooth surfaces. After three weeks' stay the patient returned home completely free of the eruption. Cortisone was continued on an ambulatory basis, 100 mg. every other day. At the end of August use of the drug was stopped for one week, during which time a relapse occurred in the form of an outbreak of new bullous lesions scattered over the trunk and involving the genitals and buttocks. Daily cortisone therapy was resumed, and the eruption subsided by the end of September. Since then the disease has become more refractory to treatment, and for the past two weeks there has been considerable progression, with deterioration of the general health. The total amount of cortisone given to date has been 14.2 gm., and side-effects have consisted of hirsutism, edema, and "moon-face."

DISCUSSION

DR. MARION B. SULZBERGER: What dose is the patient taking now?

DR. JESSE A. TOLMACH: One hundred milligrams daily.

DR. MARION B. SULZBERGER: Has anyone here seen patients who require continually increasing doses in order to maintain their remission, as though there were some sort of habituation or tolerance or acquired resistance to these hormones? I am not sure this is such a case, because if I understood correctly, the patient received 150 mg. daily at first, and now receives only 100 mg. We have begun to administer much larger doses, up to 300 and 400 mg., of corticotropin (ACTH) per day to patients with pemphigus. We started to do that when the Boston group said they had had no pemphigus which failed to respond to such initial large doses, whereas with the smaller dose we had been giving, 100 to 200 mg. a day, we had many failures. I think in this case it is worth while to go up to the limits of tolerance.

DR. J. GARDNER HOPKINS†: Our experience has been the opposite of Dr. Sulzberger's. We have had three patients who responded brilliantly at first but who, after a relapse, showed no response to the same dose. One patient has received as much as 500 mg. daily without benefit, although she previously responded well to 200 mg. Certainly, our impression is that one has to keep increasing the dose to get an effect.

DR. MARION B. SULZBERGER: Our experience has been the opposite. We have had no case in which we have had to continue to go up in the maintenance dose. Once we have arrived at an established maintenance dose for a given patient, we have been able to keep on with that dose for as long as a year and a half. It has, in fact, sometimes been possible to reduce the daily dose gradually.

DR. J. GARDNER HOPKINS: We have to remember that pemphigus is a cyclic disease. Without any treatment at all a wave of bullae will develop and later subside, and then another wave. This makes us doubtful about our observations as to changes in the requirement for cortisone.

DR. JESSE A. TOLMACH: I had been under the impression that cortisone had reached the end of its efficacy in this case. In view of the fact that the patient has pemphigus, which justifies any rational therapeutic procedure, it might be well to try increased dosages.

Lupus Vulgaris; Boeck's Sarcoid. Presented by DR. JESSE A. TOLMACH.

M. E., a man aged 37, is presented from Beth Israel Hospital. An eruption developed on the dorsum of the right hand in 1942, a lesion on the right posterior portion of the chest in 1944, and one on the right wrist in 1947.

When seen at the clinic of Beth Israel Hospital on Feb. 8, he presented a well-defined, scaling, raised, dull-red, infiltrated plaque over the dorsum of the hypothenar eminence, extending over the dorsum of the proximal two phalanges of the right fifth finger. This digit was swollen

† Dr. Hopkins died on Feb. 27, 1951.

in a fusiform manner. In the midst of the portion of this lesion overlying the proximal phalanx of the finger there was evidence of a healed sinus about 3 mm. in diameter. Over the volar aspect of the right wrist there was an oval, dull-brown-red, raised, infiltrated, tumid lesion measuring 4.5 by 2.5 cm. This lesion upon diascopy exhibited "apple-jelly nodules." On the right midposterior portion of the chest there was a similar, well-defined, irregularly shaped plaque which measured 5 by 2.5 cm.

A roentgenogram of the chest on Feb. 8, 1950, showed linear strands in the right lower lung field but no evidence of recent pulmonary disease. The heart and mediastinum were within normal limits. A roentgenogram of the right hand showed several areas of translucency with very sharp borders, suggestive of cystic areas, in the proximal phalanx of the fifth finger. There was some sclerosis of the shaft of the phalanx, with loss of the normal trabecular pattern. The phalanx also appeared somewhat shortened. The soft tissues of the proximal portion of the fifth finger showed fusiform swelling, and there was some irregularity of the cortex of the shaft of the fifth metacarpal. The remaining bones of the hand appeared normal. The findings in the proximal phalanx of the fifth finger are compatible with the diagnosis of tuberculous dactylitis. However, other causes for cystic changes cannot be entirely ruled out, such as sarcoidosis, although the remaining bones showed no abnormalities.

A second roentgenogram of the hand, on Oct. 6, showed no further changes.

Biopsy performed Feb. 10, 1950, showed beneath the epithelium, which revealed in places slight parakeratosis and in other places slight hyperkeratosis, a granulomatous inflammation occupying the upper cutis. This inflammatory process was composed of epithelioid tubercles separated by a lymphocytic infiltration. Very few giant cells were present, and no caseation was found. In some areas the tubercles tended to coalesce.

Stained smears made from the tissue were negative for acid-fast organisms.

The picture was consistent with a diagnosis of Boeck's sarcoid.

On Feb. 15, 1950, the reaction to the tuberculin test was negative in a dilution of 1 : 1,000,000 and 2+ in a dilution of 1 : 100,000.

The reaction to BCG vaccine was positive in 48 hours on March 10.

On April 17 guinea pig inoculation was negative, as was a tissue culture. The report of the biopsy was similar to that of Feb. 10. A complete blood count was normal; blood proteins and the ratio of albumin to globulin were normal, and repeated blood calcium determinations also gave normal findings.

The patient was treated with 150,000 units of calciferol from May 3, 1950, through Nov. 28, and in the seven months of this therapy slow but definite changes took place. The hand lesion lost most of its reddish scaly character and edema and became flatter. The back lesion exhibited paling in two areas and appeared flatter, only during the last two months. The lesion of the wrist was removed surgically.

On Nov. 29 one area in the lesion on the back was infiltrated with 200 mg. of dihydrostreptomycin in 2%[1] procaine hydrochloride. There was an immediate wheal followed by an eczematous dermatitic response. On Dec. 13 procaine hydrochloride alone was injected, with no reaction. On Dec. 20 the same area was infiltrated with 30 mg. of dihydrostreptomycin in 1% procaine hydrochloride with epinephrine, with no immediate reaction. One week later a small crust was seen at the site. The result of the dihydrostreptomycin injections is as yet equivocal, although less activity appears to be present in the treated site.

DISCUSSION

DR. GEORGE M. LEWIS: I had the benefit of hearing the case demonstrated by the presenter, and I agree with him that this probably is an intermediate type of tuberculosis, with good evidence that both sarcoid and tuberculosis are coincidentally present. This is a most interesting and important case, as it lends support to those who believe that these two diseases are etiologically connected.

DR. BEATRICE M. KESTEN: The only other question I had was this, could the lesion on the hand be a beginning acrodermatitis chronica atrophicans? It seems to me the location and color were right, and I thought there was definite atrophy of the subcutaneous tissue. I do not know whether the biopsy specimen was taken from this lesion.

DR. JESSE A. TOLMACH: The eruption on the hand, when first seen, was infiltrated and had almost the same appearance as the eruption now seen on the back. The roentgenologists found

it difficult to distinguish between sarcoid and tuberculous change in the involved phalanx. This man has a histologic picture of sarcoid confirmed by three pathologists. The sections were taken from the back and from the wrist. As you may have noted in the history, this patient had a positive reaction to tuberculin in a high dilution, 1 : 100,000, and a positive reaction to BCG vaccine in 48 hours, both of these indicating more tuberculous than sarcoidal reactions. The fact that only one digit is involved is also uncommon in sarcoid, in which the involvement is usually multiple. It seems that we have in this case a merging of the characteristics of tuberculosis and sarcoid. The patient responded to calciferol, curiously; the lesion on the hand subsided to a large extent, whereas the lesion on the back seemed to be very little affected.

Chronic Recurrent Miliaria. Presented by Dr. Jesse A. Tolmach.

J. L., a Jewish man aged 43, complains of an eruption of one year's duration. Prior to treatment the eruption became worse in hot weather. The trunk and extremities show discrete pinpoint- to pinhead-sized erythematous papules and vesicles. Occasionally the affected areas become eczematized.

Serologic reactions for syphilis were negative, and results of urinalysis were normal. The feces contained no blood. The patient has been studied in the ophthalmologic and neurologic clinics for various complaints, but no organic findings were demonstrated. A roentgenogram of the skull was reported as normal. Four biopsies of the skin have been performed. One report was "chronic dermatitis," but no sweat glands or ducts were found in this section. The other three sections revealed spongiosis with vesicle formation with an acute inflammatory response.

This eruption responds best to a combination of 50,000 units of water-soluble vitamin A (aquasol®) daily and treatment with infrared rays to the affected areas twice a week. Local lotions, pastes, and compresses cause the eruption to become worse. Before treatment sweat tests with bromophenol blue paper revealed no sweating in the affected areas, and a normal sweat pattern on other parts of the body. At present sweat tests show a diminished sweat response in the affected areas.

DISCUSSION

Dr. Marion B. Sulzberger: Unfortunately, the histopathology in this case does not show the characteristic picture, but it is very difficult to find a connection between the vesicles and the actual sweat glands and ducts unless true serial sections are examined. It is a very narrow duct and can easily be missed. When there is abnormal plugging of the sweat ducts, one can usually find some cause or explanation for the plugs. In other words, development of prickly heat when one works in continuous hot humid environments is the more-or-less usual phenomenon, and one does not need to assume an abnormality; but in a case such as this, in which a person manifests prickly heat without strain and stresses or sweating, one must assume some other cause for the abnormal tendency to sweat retention. Sometimes one finds it is a drug, such as quinacrine (atabrine®) hydrochloride. Sometimes it is a vitamin deficiency, an infection, a fungous infection, or another dermatosis, such as lichen planus, or a congenital anomaly. In most cases we have found that there is a fault in keratinization, and I think that is what this patient shows. He not only has the papular lesions of sweat retention and the usual findings of lack of sweating in the areas of plugged glands, but has a general dryness of the skin and a quite noticeable general fault in keratinization. There are certain forms of mild ichthyosis or xeroderma which are often, but not always, proved to be susceptible to this type of eruption upon sweating. The patient gives a history characteristic of these cases; he says he sweats profusely in other areas, e. g., face and axillas, while the involved areas remain dry. These people, when unable to pour out sweat in some areas, seem to continue to send the impulse or stimulus to pour out sweat to all the sweat glands and therefore sweat more profusely from glands which are not blocked. Another truly pathognomonic point, perhaps, which the patient described was that as soon as he starts to sweat he feels a prickling and itching sensation in the affected areas. For all these reasons and others, I agree with the theories and diagnosis of the presenter.

Dr. Jesse A. Tolmach: It is interesting to note that this patient has had repeated attacks of miliaria throughout all seasons in the past year in New York City's climate. He has been avoiding any work on the ground that any effort produces the eruption. We have been able to precipitate an attack on several occasions by merely "threatening" him with a job. He reacts with fear to such a threat, and this is accompanied by profuse sweating in unaffected areas of

the skin. The miliaria then appears, and in each attack the pattern of a fixed eruption is followed. We were unable to demonstrate plugging of the sweat ducts, and this may be due to the fact that not enough tissue sections were stained.

By exposing the patient to infrared rays three times weekly and by the administration of water-soluble vitamin A, both over a period of about two months, we were able to produce some sweating in the involved areas, which previously did not produce sweat in either active or quiescent periods.

Esthiomene (Elephantiasis of Penis and Scrotum) Due to Lymphogranuloma Venereum. Presented by DR. J. J. ELLER.

A. R., a Puerto Rican aged 50, is presented from New York City Hospital. He was admitted to the genitourinary service with a history of scrotal and penile edema of four months' duration. He stated that while he was in Georgia 20 years ago a penile discharge developed associated with bilateral inguinal buboes, which were incised and drained. He received no other treatment. He denies treatment for syphilis, but has had diabetes for seven years. He has lived in New York City for 15 years.

There were bilateral inguinal scars, edema of the penis and scrotum of huge proportions (approximately twice the present size). There was no discharge or pain. A few small, discrete, nontender nodes were felt in the inguinal region. No primary lesion was seen.

Findings from blood studies were normal, and urethral smears and serologic reactions for syphilis were negative. A roentgenogram of the chest was normal. The reaction to the Frei test for venereal lymphogranuloma was positive after 96 hours.

Study by the genitourinary department revealed no evidence of past or present Neisserian infection. No urethral strictures were present. Because of the patient's difficulty in urinating, a "dorsal slit" was performed, and no lesions of the glans penis or prepuce were exposed. Rectal examination revealed no strictures or proctitis. Extensive blood studies could demonstrate no microfilariae. A medical consultant could account for the edema on no other basis than lymphogranuloma venereum.

Two weeks ago the patient was treated with aureomycin, 500 mg. every six hours, and the penis and scrotum have decreased to about half their former size.

DISCUSSION

DR. DAVID BLOOM: The scars in the inguinal region are due to an operation performed 20 years ago, but the edema of the scrotum and penis is of a few months' duration only. It is probable that the edema has nothing to do with the previous infection. This edema may have been brought on by some infection other than lymphogranuloma venereum.

DR. HANS BIBERSTEIN: I think there is a connection and that it is most probably due to the lymphopathia which he had. In a patient whose case I published with Barthels many years ago, "edema" also developed 10 or 11 years after a lymphogranuloma venereum infection (Beitr. klin. Chir. **152**:325, 1931). On the basis of a histologic examination we concluded that this was not a sequela but an active process. At that time we had no sulfonamide drugs or antibiotics and so suggested conservative treatment, hoping that there would be a medicament sometime which would have an effect on the virus and would be able to improve if not cure the condition.

DR. DAVID BLOOM: In the few cases I have observed, edema of the penis and scrotum was associated with lymphadenopathy in the pelvis and with rectal stricture. I think particularly of a patient I saw at the Veterans Administration Hospital through the courtesy of Dr. Howard Fox. This case came to autopsy and showed, in addition to a marked stricture of the rectum, considerable lymphadenopathy of the pelvis. The patient presented tonight has no anorectal involvement.

DR. WILLIAM CURTH: I have followed for 15 years a patient with lymphogranuloma venereum, in whom recurrent attacks of iritis later developed for which no other cause could be demonstrated, and who responded favorably to aureomycin also.

Chronic Discoid Lupus Erythematosus; Purpuric Eruption of Lower Extremities (Pigmented Purpuric Lichenoid Dermatitis of Gougerot and Blum?). Presented by DR. J. LOWRY MILLER.

Case for Diagnosis: Dermatitis Herpetiformis? Presented by DR. HANS BIBERSTEIN.

Paul Gross, M.D., *Chairman*

Anthony C. Cipollaro, M.D., *Secretary*

Feb. 6, 1951

Xeroderma Pigmentosum (Exhibiting Skin Reactions in the Shorter Ultraviolet Wave Lengths). Presented by DR. BEATRICE M. KESTEN and DR. MEYER H. SLATKIN.

R. W., a Haitian boy aged 21 months, is presented from Vanderbilt Clinic with skin pigmentation of nine months' duration. Delivery was normal. The child was taken out in the sun at the age of one month and cried. Each time thereafter he cried when he was left in the sun, and when he was old enough to walk he always avoided sunlight. Photophobia was noted at about the age of 9 months, and this has increased until now the child shuts his eyes or hides his head on a sunny day if he is facing the light.

At about the age of one year the parents noted slight reddening of the skin on the face and dryness and freckles on the face and scalp. These have increased in number and slightly in size and depth of color.

The patient's general health has been good. He has a fair appetite but dislikes milk.

The father and mother are fifth cousins once removed. The common ancestor was a native of Poland who married a Haitian woman. The progeny have been natives of Haiti. None has had red hair or blue eyes. The mother and father are lighter in color than the patient, as is his only brother, aged 6 years. All are in good health, and there is no family history of xeroderma pigmentosum.

The patient is of average size and weighs 22 lb. (9,980 gm.). He has medium-dark-brown skin and curly brown hair. Dentition, nails, and mucous membranes are normal. The involved areas are the scalp, face, ears, neck, posterior aspect of the trunk, and lateral surfaces of the arms. The scalp shows numerous small dark-brown and black pigmented spots. The skin of the face is dry, slightly erythematous over the outer aspect of the cheeks, and covered with brown and black freckles from 1 to 3 mm. in diameter. On the posterior aspect of the trunk and lateral surfaces of the arms the skin is slightly darker than on the face; in areas there is a fine desquamation, and numerous depigmented specks are mingled with some freckling. There is a Mongolian spot over the fourth and fifth lumbar vertebrae. The skin is of normal thickness, and there are no telangiectases or growths.

Ophthalmologic examination by Dr. G. Bruce revealed no abnormalities.

The urine was normal, with absence of porphyrin. The blood count showed 11.2 gm. of hemoglobin and 7,100 white blood cells, with 42% polymorphonuclear leucocytes, 48% lymphocytes, and 6% eosinophils. The Wassermann reaction of the blood was negative. Blood sugar was 82 mg. per 100 cc. The blood type was A Rh-positive. The vitamin-A and carotene levels of the blood were normal. Roentgenologic examination of the pelvis and teeth revealed no abnormalities.

Sections of moderately pigmented scaly skin from the right cheek showed hyperkeratosis which was somewhat more marked in the region of a follicular infundibulum. The granular layer was wide. There was edema of the basal layer which appeared to be depleted of melanin. Some of the cells were larger than normal. The rete had been flattened out. In the subepidermal cutis there were many chromatophores and an increase of mononuclear cells which surrounded blood vessels. Many of the vascular channels were greatly dilated.

Histologic examination of a deeply pigmented freckle from the left cheek showed moderate hyperkeratosis and a very wide granular layer. The epidermis was edematous, particularly along its basal layer. There was depletion of melanin. Some of the deeply seated epithelial cells were increased in size. A few contained multiple nuclei. These changes suggested anaplasia, to a slight degree. There were numerous chromatophores in the subepidermal cutis which disclosed vascular dilatation, perivascular edema, and cellular infiltration. Sections stained with dihydroxyphenylalinine showed numerous melanoblasts which were packed side-by-side and seemed to replace, in part, the basal layer. Large numbers of chromatophores appeared in the subepidermal cutis.

Sections of skin from a pigmented area on the right shoulder containing white specks disclosed a moderate loose hyperkeratosis. There appeared to be slight acanthosis with some edema of the epidermis. The granular layer was distinct. Melanin was difficult to identify in

the epidermis. Many chromatophores were seen in the subepidermal cutis which showed slight perivascular edema and an increase in spindled mononuclear cells. The diagnosis was xeroderma pigmentosum.

The effects of light rays are presented in the accompanying tables.

TABLE 1.—*Effect of Light Rays*

Source of Light	Time of Exposure	Area Exposed		Results	
		Exposed	Uninvolved		
Winter sun	1 min.	Face	.....	Photophobia	
Winter sun through window glass	1 min.	Face	.....	Photophobia	
Grenz ray (erythema 150 r)	25, 50, 75 r	Face, right shoulder	Right leg (lateral)	0	
				Exposed	Uninvolved
Burdick Quartz Lamp (erythema, light skin 2 ft., 30 in.)	10, 20, 30, 45, and 60 sec.	Face or left shoulder	Left leg (lateral)	0	0
Kromayer Quartz Lamp (erythema, dark skin 10 in.)	10, 20, 30 sec.	Upper back	Left thigh (lateral)	Erythema and pigmentation	0
Kromayer Quartz Lamp	30 + 45 sec.	Right side forehead	Left thigh (medial)	0	0

TABLE 2.—*Effect of Kromayer Lamp, Thirty Seconds with Interposed Filters, on Involved Area, Left Side of Back*

	Reaction
Left half of circle, with filters	.....
791 (2100-7400 A.)	Erythema and pigmentation
986 (2200-4200 A.)	Erythema and pigmentation
970 (2600-7400 A.)	Erythema and pigmentation
774 (2800-7400 A.)*	0
W. G. (3130-7400 A.)	0
3850 (3600-7400 A.)	0
3384 (4900-7400 A.)	0
Right half of circle, without filter	Erythema and pigmentation

* Filter 774 was repeated with five-minute exposure with no reaction.

TABLE 3.—*Effect of Kromayer Lamp, Thirty Seconds with Interposed Sun Screens, on Involved Area on Right Side of Back, Jan. 31, 1951**

Sun Screen	Reaction
10% Titanium oxide ointment	0
A. filter	0
"Skolex"	0
Tripelennamine hydrochloride cream	Erythema
Tripelennamine hydrochloride ointment	Erythema
Diphenhydramine hydrochloride cream	Erythema
10% "Sunarome" VV in alcohol	Erythema
15% *p*-aminobenzoic acid in alcohol	Erythema

* On Feb. 5 the test was repeated on left and right side of trunk using first six sun screens with control areas on each side. On Feb. 6 there was no reaction except to controls.

DISCUSSION

DR. DAVID BLOOM: Dr. Kesten should be commended for presenting such a well worked-up case. From the history I could not understand whether the child has reacted to a special range in ultraviolet light and whether the reaction to soft rays was positive. It should not be surprising that this child alone has this disturbance, as xeroderma pigmentosum is a recessive disease. Consanguinity of the parents, as in this case, is a finding in a high percentage of such

cases. The presence of this abnormality in Negroes indicates that it does not consist merely of simple sensitivity to light, but that there is a fundamental disturbance of the epidermal cells behaving abnormally, like the skin of old people.

DR. CHARLES WOLF: Would Dr. Kesten describe the treatment? These are pitiable cases, and we have been helpless in the past. I wonder whether corticotropin (ACTH) or cortisone might be employed.

DR. J. GARDNER HOPKINS†: The term hypersensitivity to light should be used with reservation in regard to this disease. That these patients are not hypersensitive to light in the ordinary sense is well illustrated in this case in which rather an excessive exposure to ultraviolet rays was required to produce erythema. It is more of an altered reaction to light. Whether that is another form of hypersensitivity, that is, a delayed reaction with hyperkeratosis and disturbance of pigment, is a question. The atrophy and keratosis which these patients exhibit would not be exhibited by a normal person except after years of chronic exposure to light. That seems to be quite different from the thing we ordinarily speak of as light sensitivity. The determination of zone susceptibility is both interesting and practical. As Dr. Kesten has brought out, it is possible to protect this child's eyes by knowing the range of light to which he is sensitive. It has changed the attitude of the infant from one who is terrified to one who peers around normally, and I think it is possible that the same determination will make it possible to devise a sun screen that will give effective protection to the skin.

DR. BEATRICE M. KESTEN: This child is of interest for several reasons: First, he lives in Haiti; second, he is very young, and it is unusual to see a child of 21 months with a well-established xeroderma pigmentosum, and, third, he is largely Negro. In answer to Dr. Bloom, the parents are no more than "kissing cousins"; I don't know whether you can speak of the disease being recessive in this case. The child has marked photophobia to sunlight but looks directly at the Kromayer lamp when it is a few inches from his face. He has been fitted with special glasses which filter out ultraviolet rays and is now able to keep his eyes open in direct sunlight. As to the skin, we are not very clear as to his reaction to light. It was difficult to produce an erythema to rays by the Kromayer lamp. He is no more reactive than two controls of his age with similarly colored skin. By use of Corning light-transmitting filters, the erythema and pigmentation, as reported previously, are produced by light rays below 3,100 A. This erythema could be prevented by applying various antiactinics to the skin. As for protecting the skin, we had in mind *p*-aminobenzoic acid, to be given internally as well as applied to the exposed areas; large doses of vitamin A, to see if we could make the epidermis a little more resistant to sunlight, and the avoidance of green vegetables.

Discoid Lupus Erythematosus Treated with Cortisone (with Unusual Familial History). Presented by DR. J. GARDNER HOPKINS.†

M. P., a Jewish woman aged 26, is presented from the Vanderbilt Clinic with an eruption on the face, of one and one-half years' duration. In the latter part of the summer of 1949, while vacationing at a beach, the patient noticed small reddened areas over the bridge of the nose, cheeks, and forehead. Swelling and cracking of the lips began in the summer of 1950. She was seen by various doctors; antihistaminic drugs, intravenous calcium therapy, and oral bismuth therapy were given without benefit. Protective creams were used, as the patient had noticed accentuation of the areas on exposure. Menstrual periods had been accompanied by an exacerbation of the eruption. At the age of 15 the patient first began to have transient erythema of the face lasting two to three days. These episodes accompanied emotional upsets or brief physical illnesses.

The mother has had lupus erythematosus of the discoid type for approximately 15 years. A maternal first cousin of the patient, a woman aged 44, has had lupus erythematosus of the subacute disseminate type for the past two years, and she has recently been treated at Lenox Hill Hospital with steroid therapy.

When the patient was admitted to the hospital on Dec. 14, 1950, there were 12 round and oval areas of erythema with scaling, telangiectasia, and patulous follicles over the "butterfly" area of the face. The size of these lesions varied from 2 by 1 cm. to 0.5 by 0.5 cm. The largest was over the bridge of the nose. The lips were fissured, edematous, and scaling. The general physical examination revealed no significant abnormalities.

† Dr. Hopkins died on Feb. 27, 1951.

Serologic reactions for syphilis were negative. A hemogram was normal. The erythrocyte sedimentation rate was 9 mm. per hour (Westergren). The fasting eosinophile count was 175 per cubic millimeter and four hours after administration of epinephrine hydrochloride it was 19 per cubic millimeter. The total serum protein was 6.9 gm. per 100 cc. with a normal ratio of albumin to globulin. The urea nitrogen was 16 mg. per 100 cc. The basal metabolic rate was —33%. The urine contained porphyrin. Porphyrins were not demonstrated in the urine of the mother and maternal first cousin. An electrocardiogram was normal. A roentgenogram of the chest showed only a small area of calicified scarring in the left hilar region.

Examination by Dr. G. F. Machacek of a biopsy specimen disclosed an atrophic epidermis which, however, had undergone hyperkeratosis and moderate parakeratosis. Follicular infundibula disclosed small, compact, keratinized plugs. There was a leucocytic infiltration among the lamellae of the stratum corneum. The atrophic epidermis showed degeneration of the deeper layers. Mononuclear-leucocytic infiltration involved both the epidermis and the cutis. Some of the capillaries were dilated. Although he found the histologic picture atypical, Dr. Machacek nevertheless concurred in the clinical diagnosis of lupus erythematosus.

From July 21, 1950, through Dec. 8 the patient recevied 450 mg. of gold sodium thiosulfate in the clinic; after the fifth injection localized areas of pruritus occurred. Prior to subsequent injections tripelennamine hydrochloride was administered without further occurrence of post-injection pruritus. The lesions responded slowly, but new lesions appeared during the treatment.

Cortisone therapy, 300 mg. intramuscularly, was begun on Dec. 18. On the second day 200 mg. was administered and 100 mg. thereafter through the 14th day. At the end of 72 hours the erythema was less pronounced; on the 14th day only the large scaly lesion on the bridge of the nose remained. The dosage was reduced to 100 mg. three times a week for one week, and then to 50 mg. three times a week for the following week, at which time definite recurrence of erythema over the butterfly area of the face took place, with scaling and fissuring of the lips. The patient has received 100 mg. of cortisone a day since Jan. 29, with only slight improvement thus far.

DISCUSSION

Dr. E. T. Bernstein: I would suggest that the patient be treated with testosterone, perhaps 50 mg. a day, because a recent publication in *The Journal of the American Medical Association* reported favorable results, particularly with the chronic discoid localized and disseminated types of lupus erythematosus. I now have had a patient under treatment with testosterone for about two months, and it is my impression that there has been improvement. Of course, lupus erythematosus may be self-limited.

Dr. Maurice J. Costello: In my experience, cortisone is a wonderful drug while it is being administered in the treatment of disease. I have seen lesions of lupus erythematosus of the profundus type almost disappear under cortisone therapy, only to reappear promptly when it was discontinued, and the last state in several cases was worse than the first.

Dr. J. Gardner Hopkins: This patient perhaps should be presented as an excellent way to waste cortisone. She responded beautifully to 200 mg. a day, cleared up, and looked well. Then we began to reduce the dose and tried various schedules, the last about 100 mg. a day. Our general experience with other diseases has been that to keep on with a dose that is not promptly effective is throwing the hormone away. If we doubled up and gave 200 mg. a day, we would probably use less cortisone in the long run. What can be done permanently, of course, we do not know, because it is just as discouraging as Dr. Costello said. From what we have seen in some other cases, I believe it should be possible, after the patient is clear, to slowly reduce the amount and frequency of the injections. If we do not stop the moment she is clear and resume good effective doses the minute there is a relapse, I am very hopeful we can cope with the disease. The family history is intriguing, but I presume that it is a coincidence.

Dermatitis Herpetiformis; Prurigo Nodularis; Fixed Drug Eruption (Phenolphthalein). Presented by Dr. Leo Schweich.

J. A., a Greek man aged 85, is presented from Vanderbilt Clinic with the following complaints: (1) itching bumps on the legs and arms, of about 15 years' duration; (2) itching blisters on the body generally, of 3 months' duration, and (3) increased pigmentation on the cheeks.

About 15 years ago intensely pruritic nodules developed on the extensor surfaces of the arms and legs. Since 1942 topical applications were used but afforded little relief. Three months

ago there developed groups of pruritic papules, vesicles, and a few bullae on the palms, soles, extremities, scalp, lips, oral mucosa, and trunk. He was first seen at Vanderbilt Clinic on Oct. 19, 1950. X-rays and other physical energies have never been used. No one else in the family has skin trouble. On Dec. 28 a number of fairly sharply defined, brownish-grayish macules were seen on the face, neck, and right hand. The patient admitted having taken a laxative containing phenolphthalein (ex-lax®) occasionally over a period of years.

On Oct. 19 there was a generalized eruption involving the scalp, palms, soles, and oral mucosa, consisting of grouped papules, vesicles, and a few bullae. Secondary lesions in the same areas were crusts, excoriations, and scars, with hyperpigmentation at the sites of healed lesions.

The lesions of long standing were those on the extensor surfaces of the arms and legs, and a few on the upper part of the back. These consisted of excoriated, depigmented nodules and papules measuring up to 1.5 cm. in diameter and accompanied by very little erythema. Most of these nodules were irregularly spaced.

On Dec. 28 a number of dime-sized, fairly sharply defined, brownish-grayish macules were noted on the face, neck, and right hand.

Serologic reactions for syphilis were negative. The blood count and results of urinalysis were normal. The reaction to a patch test with 50% potassium iodide was negative.

Biopsy of a nodular lesion on the back disclosed an epidermis which was locally acanthotic and in some sections disclosed prominent peg-like penetrations within the cutis. Hyperkeratosis was localized, as also was a widening of the granular layer. Some sections disclosed an intraepidermal and subepidermal vesicle-pustule. This was surmounted by parakeratosis. Between the lamellae cocci were present. The cutis beneath this area was scarred. An increase of vessels was almost angiomatous in appearance. Numerous polymorphonuclear leucocytes were seen. The diagnosis was compatible with prurigo nodularis with scarring.

Tripelennamine hydrochloride (pyribenzamine®), 150 mg. daily, and later diphenhydramine hydrochloride (benadryl®), 50 to 100 mg. daily, were taken for one month without benefit. The use of these drugs was discontinued on Dec. 7, and sulfapyridine, 1 gm. daily, was prescribed. The lesions of dermatitis herpetiformis ceased itching and have improved progressively since that time. The prurigo nodularis lesions continue to itch and have remained unchanged. One was treated with solid carbon dioxide without improvement. The hyperpigmented macules on the face, neck, and right hand have increased in size during the past three weeks, in spite of the fact that the use of the laxative containing phenolphthalein was discontinued. Other than sulfapyridine, no medications are now being used.

DISCUSSION

DR. MAURICE J. COSTELLO: Dr. Schweich might have suspended the sulfapyridine and proved the diagnosis. The case is certainly unique. Prurigo nodularis and dermatitis herpetiformis in themselves are uncommon. The ocurrence together is truly a rarity.

DR. E. T. BERNSTEIN: I thought the patient exhibited neurotic excoriations. For the diagnosis of prurigo nodularis might be substituted that of neurodermatitis of the hypertrophic type occurring within reach of the hands. My diagnosis would be neurodermatitis in an old man, simulating dermatitis herpetiformis, because of the polymorphicity of the lesions, which consist of ruptured vesicles, papules, and other grouped lesions, accompanied by pigmentation.

DR. LEO M. SCHWEICH: At the time of his first visit to the clinic this patient presented two distinct types of eruption, one more acute, of about three months' duration, consisting of vesicles and bullae, grouped and located over the shoulders, neck, face, and scalp. While there was no improvement subjectively or objectively during treatment with diphenhydramine hydrochloride, this eruption cleared almost dramatically under sulfapyridine therapy within a few weeks. The other type of eruption was nodular and had existed for about 15 years; it was located on the extensor surfaces of the extremities, on the buttocks, and on the trunk, and consisted of discrete, firm, semiglobular, partly scaly lesions which were surrounded by infiltrated and, in some areas, almost fibrotic skin with areas of depigmentation and hyperpigmentation. Because of its chronic course, the clinical picture, and the histologic findings, I believe these lesions to be representative of prurigo nodularis. On his last visit the patient exhibited in addition a number of sharply defined, grayish-blackish discolored macules on the face and neck; a few similar lesions, located on the right hand, presented a typical cockade-

shaped arrangement with annular zones of pigmentation, an expression of the local variations in sensitivity to the drug. Upon questioning, the patient admitted having taken a laxative containing phenolphthalein for some time.

Incontinentia Pigmenti (?) Associated with Hydrocephaly. Presented by Dr. J. Lowry Miller.

J. F., a girl aged 19 months, is presented from Vanderbilt Clinic with "fountain-spray" areas of alternating hyperpigmentation and normally pigmented skin on the trunk and extremities, present since birth. Shortly after birth a bizarre pattern of pigmentation was noted on the trunk and extremities. The infant was unable to suck at first and did not develop normally. She is the first child of normal parents, delivered without instruments at full term, and the mother (blood type A Rh-positive) gave no history of illness during pregnancy. Convulsions occurred in May, 1950, and pneumoencephalograms at Kings County Hospital revealed arrested hydrocephaly.

On the trunk and extremities there are irregular bands of hyperpigmentation and alternating areas of normal skin in bizarre patterns. The pigment is light-brown and becomes tan on the abdominal wall. There is no change in the texture of the skin and no follicular atrophy, alopecia, or inflammation.

Serologic reactions for syphilis were negative. Urinalysis revealed no albumin or sugar. The blood picture was normal.

Biopsy showed slight increase of keratinization. A large portion of the epidermis, however, had been torn away. The granular layer was represented by a single line of keratohyalin cells. There appeared to be a slight edema in the epidermis. The basal layer contained some melanin which was for the most part inconspicuous. In the corium an increase of cells was seen in the perivascular areas. Coil glands and hair follicles disclosed no remarkable changes. About some of the hair follicles there was some increase in fibrous elements. No chromatophores were present. Dihydroxyphenylalanine-stained sections showed numerous melanoblasts which appeared to be scattered along the basal layer at fairly regular intervals. It was not possible to make a histologic diagnosis of incontinentia pigmenti.

With glutamic acid hydrochloride therapy, 250 mg. a day, there has been some improvement in the child's response, and she is now able to roll over unassisted. The cutaneous lesions are unchanged.

DISCUSSION

Dr. Frederick Reiss: The few cases of incontinentia pigmenti I have seen did not show such a widespread hyperpigmentation. Moreover, the eruption affecting the flanks was in the form of bizarre-shaped plaques. In this case the histopathologic picture does not bear out the presenting diagnosis. There is no increase of chromatophores in the cutis. I believe the hyperpigmented areas represent the normal skin and that the light skin is depigmented.

Dr. Helen O. Curth: I thought the pattern was rather typical, as were the sex of the child and the combination with another congenital malformation.

Dr. J. Gardner Hopkins: The pattern did suggest incontinentia pigmenti, but the streaks were not quite as zebra-like as are usually seen. On Dr. Machacek's evidence I would have to call it incontinentia pigmenti. It does raise the question whether there may be different stages of this pigmentary anomaly and whether study of this case later on would show loss of pigment in the basal layer and collections of chromatophores.

Dr. David Bloom: I had the opportunity to observe four or five cases of incontinentia pigmenti in children, in addition to those in adults. In all the children there was a similar pattern of hyperpigmentation arranged in a wavy manner on the trunk and extremities. In some of them for whom histologic examination has been performed, the typical picture of numerous chromatophores in the corium was found. This is responsible for the slate-gray color which is usually seen in incontinentia pigmenti. In this patient the color was not gray but brown. This explains why the pathologic examination did not reveal any chromatophores deep in the corium. It is quite possible, as Dr. Hopkins suggested, that in early stages the pigment is still present in the basal-cell layer and later drops down to the corium. It is therefore possible that the color of this eruption will change into the typical color seen in incontinentia

pigmenti. At present, therefore, we are justified in calling it a systematized pigmented nevus rather than incontinentia pigmenti.

DR. J. LOWRY MILLER: The reason for presenting this child was that the histology did not confirm the clinical diagnosis of incontinentia pigmenti. We plan to do a series of biopsies. In the future it may be shown that we did not do the biopsy in the right place now, or, as Dr. Hopkins suggests, it may turn out to be an incontinentia pigmenti in which the pigment has not dropped to the cutis.

Dermatitis Medicamentosa (Lichen-Planus-Like Lesions) Due to Gold Therapy. Presented by DR. DARNEY MOON-ADAMS.

Lichen Planus-Like Dermatitis Medicamentosa? Presented by DR. DARNEY MOON-ADAMS.

NEW YORK DERMATOLOGICAL SOCIETY

J. Gardner Hopkins,† M.D., *President*

Anthony C. Cipollaro, M.D., *Secretary*

Jan. 23, 1951

Eczema Threatening Integrity of Skin Graft. Presented by DR. GEORGE M. LEWIS.

J. M., a boy aged 13, presented himself at the dermatology clinic of New York Hospital with dermatitis of the lower extremities of four months' duration. Three months prior to the appearance of the eruption the scar tissue of an old burn had been replaced by split-thickness grafts. He failed to respond to mild local medicaments and even became worse. All possible contact irritants were ruled out, and a biopsy was performed.

There is an erythematous, scaling, and exudative dermatitis confined to the site of the skin grafts.

Urinalysis showed no abnormalities, and the hemogram was within normal limits.

Biopsy showed the epidermis to be tremendously acanthotic with elongation of the rete pegs. Psoriasiform areas of parakeratosis were seen. Marked intracellular and intercellular edema was present. The granular layer was thin or absent. Numerous small vesicles were seen in the upper epidermis. The epicutis was markedly edematous, with a diffuse infiltrate of small round cells, wandering connective-tissue cells, polymorphonuclear cells, and chromoplaques of Unna. The diagnosis was granulation tissue failing to organize, acting as a foreign body to the epidermis.

DISCUSSION

DR. FRANK E. CORMIA: Because of this tendency to granulation tissue and because of the beginnings of autoeczematization on the old scars on the back, I would suggest the administration of corticotropin (ACTH), which will decrease the granulation tissue and promote epithelization.

DR. ANTHONY C. CIPOLLARO: This is certainly a very rare occurrence. Evidently there is some allergen at play here that we know nothing about. Whether the condition is due to some of the chemicals used in preparing the grafted skin would be difficult to determine. There is no question that it is a sensitization phenomenon of some kind.

DR. FRANK E. CORMIA: I did not realize that homologous grafting had been done. It is well known that when a graft from a donor is performed for a second time a specific immunologic state is present and the breakdown of the second graft is greatly accelerated. This reactive state has been induced in rabbits by Medawar by intradermal injection of blood leucocytes, which are thought by Esplin and me to carry antigenic material in autoeczematous processes. Because of the fact that this boy does have autoeczematization on the back, it might be an explanation for the peculiar reactivity present.

DR. EUGENE F. TRAUB: Dr. Lewis remembers that years ago at the New York Skin and Cancer Hospital petrolatum gauze was employed, and some of the men used silver foil as a dressing for burns, and in those days one practically never saw this type of reaction. I believe you may find that the surgeons used either sulfonamides or some similar drugs to protect the graft area from becoming infected while it was healing, and that may have started this process.

† Dr. Hopkins died on Feb. 27, 1951.

DR. J. GARDNER HOPKINS: I suppose the bacteriology in that area has been studied. Although the condition looks eczematous, I do not think you can assume immediately that it is an allergic phenomenon, although it probably is. The donor site shows marked keloid formation, and I am wondering whether that has anything to do with it. There is certainly a definite ridge at the edge of the grafted area. Is it possible that a sensitization phenomenon occurs in a heterogenous graft?

DR. EUGENE F. TRAUB: Dr. Hopkins' point about keloid formation is good; there is considerable keloid formation taking place in those areas. I would treat the area locally with continuous potassium permanganate baths, if it can be done.

DR. GERALD F. MACHACEK: I agree that corticotropin or cortisone should be tried. However, when I thought of suggesting it, I thought of the effect it might have upon the connective tissue and the epidermis. I understood that biopsy showed hyperplasia of the epidermis, and cortisone can stimulate verrucous proliferation in corns. The child has had not only autogenous but also heterogenous grafts, and the mother has a hypersensitivity. I believe it is a definite case of sensitization and that cortisone or corticotropin should be tried.

DR. WILBERT SACHS: I did not know about the transplants from the mother, but, as Dr. Lewis pointed out, the process looked like a foreign-body reaction with granulation tissue and with no attempt at organization. From that point of view I would be against corticotropin, as there is already no development of collagen and certainly would be none with corticotropin. However, the eruption is tremendously improved, at least 50% over nine days ago; so I would suggest that the present therapy be continued.

DR. FRANK E. CORMIA: The patient may be sensitive to his own epidermal tissue as well as to the homologous graft, as shown by the development of distal autoeczematization.

DR. GEORGE M. LEWIS: As mentioned, there has been considerable improvement, rather more than 50%. My impression when I first saw the patient was nummular eczema with autoeczematization. Dr. Sachs' interpretation of the slide made us reconsider. We did not employ corticotropin or cortisone for the reasons mentioned. There have been only homologous grafts recently. The skin from the mother was taken some years ago. The improvement is so striking that we plan to continue the therapy now being used.

Tuberculosis Cutis Lichenoides; Neurodermatitis. Presented by DR. ANTHONY C. CIPOLLARO.

E. G., a Negro child aged 3½ years, was first seen in the New York Polyclinic Medical School and Hospital on May 23, 1950, for an eruption on the neck, chest, and scrotum. The parent stated this had been present for three months (total duration now, approximately one year). The eruption is pruritic, and the boy is continually scratching the scrotum. At the first visit there was secondary pyoderma. The father has severe hay fever.

The child is husky, well-nourished, and intelligent-appearing. The eruption consists of discrete, scattered pinhead-sized papules on the front and sides of the neck. On the back of the chest, buttocks, chin, and right upper arm are coin-shaped areas of small, grouped, lichenoid or follicular papules about 4 mm. in diameter. These grouped lesions are fairly well marginated but have little or no scale. The scrotum is eczematized, lichenified, fissured, and slightly crusted.

The reaction to the tuberculin test, in a dilution of 1:100,000, was negative. Roentgenograms of the chest were normal.

Diagnosis from biopsy of a specimen from the back was reported as possible neurodermatitis.

The patient has been treated with salicylic acid and crude coal tar in petrolatum, elixir diphenhydramine (benadryl®) hydrochloride, and bacitracin. Response to medication as far as itching is concerned has been poor. The pyoderma has cleared. The lesions on the left shoulder may be somewhat flatter, but there has been no change on the scrotum. In general, the lesions have tended to remain stationary despite continuous coal tar and salicylic acid therapy.

DISCUSSION

DR. GEORGE M. LEWIS: Possibly it is a type of disseminated neurodermatitis in children.

DR. WILBERT SACHS: When I first saw the case I thought of lichen nitidus or lichen scrofulosus, but results of all examinations were normal, and there was no evidence in the microscopic picture of either. All we saw was a neurodermatitic reaction. The child also has a

neurodermatitis on the scrotum, which is also in favor of the diagnosis. The rest of the eruption may be a follicular neurodermatitis.

DR. MAURICE J. COSTELLO: I have seen a number of these cases through the years, in which there are patches of shiny, cohesive, and coalescent papules on the body, not often with associated pruritus, but extremely difficult to get rid of. Histologic examination does not help, as a rule. From the clinical point of view we could call it folliculopapuloneurodermatitis, if it is associated with the hair follicles. The fact that this patient also has a scrotal neurodermatitis lends some weight to the diagnosis.

DR. FRANK E. CORMIA: I agree with Dr. Costello and think we should recall the tendency of Negroes to react, particularly around the hair follicles. I think it is neurodermatitis, especially because of the scrotal lesions.

DR. ANTHONY C. CIPOLLARO: The weight of evidence favors a diagnosis of neurodermatitis, because of the biopsy report and because of the eczema of the scrotum. If this child did not have the latter, it would be extremely difficult to classify. When I first started in dermatology, some of the older dermatologists used to call this lichenoid dermatitis, which probably meant this form of localized neurodermatitis, as we call it today. Nevertheless, in Negro children who have a small papular eruption of a discrete and coalescing type, we must always consider lichenoid tuberculosis, or lichen scrofulosus. The negative tuberculin reaction does not speak against the diagnosis of tuberculosis, because we must remember that in children a negative reaction to tuberculin in a dilution of 1 : 100,000 is not significant. We expect to get a negative reaction in much lower dilutions in children. I think this case bears watching because it may turn out to be more than neurodermatitis, but for the present I go along with that diagnosis.

Scleroderma; Acrosclerosis. Presented by DR. MAURICE J. COSTELLO.

L. A., a woman aged 31, who lived in Germany most of her life and who at one time was a champion swimmer, now presents an advanced condition of scleroderma with severe acrosclerosis, with recurring multiple perforating ulcers on the already-shortened fingers. This patient was presented previously at the Manhattan Dermatologic Society as having improved greatly with a high-protein diet and large doses of diphenhydramine (benadryl®) hydrochloride. The condition of the skin covering her body and extremities has not recurred, but the acrosclerosis has continued to progress. The patient is presented for suggestions as to therapy. She already has had a bilateral cervical sympathectomy, with a resulting bilateral Horner's syndrome.

DISCUSSION

DR. GEORGE M. LEWIS: It is interesting that the lesions of acrosclerosis did not improve with the scleroderma. This might be a point in favor of differentiating some of the types of scleroderma. It would seem then that some of these hand and foot sclerodermas are different from the generalized type. In this patient the improvement is definite. Contrary to the negativistic attitude of many that we should attribute such improvement to the natural course of events, I think our therapy has been improved considerably with the antihistaminic drugs, tocopherols, diet, and other agents. As to the advisability of amputation, I wonder whether the patient would begin to have trouble in the stumps. I would, in any case, advise against amputating more than one finger as an experiment.

DR. WILBERT SACHS: As long as she has sclerosis there, and I believe the distal portion shows more intense sclerosis, I wonder whether injection of bee venom, as in Dr. Peck's case, might not be of value. We did have one patient who improved under that treatment, but the trouble later recurred.

DR. FRANK E. CORMIA: Dr. Lewis' remarks are interesting, and I agree with everything he said. Personally, I think it is a difficult problem, not only from the standpoint of treatment, but from diagnosis as well. I have always been a little confused by attempts to differentiate sharply between acrosclerosis of Sellei and generalized scleroderma. The patient has scattered lesions of scleroderma and evidence of vasospastic phenomena as well. The ulcerative lesions might be extremely difficult to treat. Corticotropin might help to heal the ulcers, but it does not afford any permanent relief in scleroderma.

DR. ANTHONY C. CIPOLLARO: This patient has already had vasodilators, and I should like to see that type of therapy pursued further. There is no question that some patients with acrodermatitis and Raynaud's syndrome have been helped by methacholine chloride iontophoresis,

and that would be a practical approach. Along with that I would be inclined to use sodium nitrite, which is an excellent vasodilator without any bad side-effects. It can be given intravenously every day or every other day. Also, I would go along with small doses of nicotinic acid several times a day, also an excellent and safe vasodilator. I would prefer this procedure to amputation because I believe it would help not only the local condition but also the disturbed vascular status which this patient also has. There might possibly be a congenital disturbance, such as a cervical rib, causing a scalenus anticus syndrome, which might cause symptoms in the fingers. Operation for removal of cervical ribs is very simple.

DR. WILBERT SACHS: It would not be difficult to fit glass cups to the fingers, start with a very low negative pressure, and increase this gradually, that is, use a modified Bier hyperemia.

DR. ANTHONY C. CIPOLLARO: There is such an apparatus on the market.

DR. MAURICE J. COSTELLO: This patient has impressed upon me the importance of the fingertips. Without them you can do nothing. This woman is ambitious, wants to get well, and cannot do a thing. She has no cervical ribs. The only thing that seemed logical was histamine by iontophoresis. She got such engorgement following that treatment that the pain was excruciating. She has had many vasodilators without effect.

A Case for Diagnosis: Xanthoma? Fibromatosis? Presented by DR. LESLIE P. BARKER.
Keratoderma Punctata Palmaris et Plantaris. Presented by DR. FRANK E. CORMIA.
Papulonecrotic Tuberculid; Erythema Induratum. Presented by DR. LESLIE P. BARKER.
Vogt-Koyanagi Syndrome. Presented by DR. J. LOWRY MILLER.
Follicular Neurodermatitis. Presented by DR. WILBERT SACHS.
Scleroderma. Presented by DR. GEORGE M. LEWIS.
A Case for Diagnosis: Granuloma Annulare? Necrobiosis Lipoidica Diabeticorum? Presented by DR. GEORGE M. LEWIS.
Secondary Syphilis (Cutaneous Relapse). Presented by DR. EUGENE F. TRAUB.

J. Gardner Hopkins, M.D.,† President
Anthony C. Cipollaro, M.D., Secretary
Feb. 27, 1951

A Case for Diagnosis: Periarteritis Nodosa? Presented by DR. J. GARDNER HOPKINS.

J. B., a man aged 23, is presented from the Veterans' Administration Hospital, Bronx, N. Y., with an eruption of the hands, feet, and face, of seven months' duration. The lesions are of short duration, disappearing within a week, but others of the same general nature continue to appear. Petechiae have appeared on the soles. One sees erythematous and purpuric papules on the palms and fingers, accompanied by pruritus and a feeling of "tightness of the skin." Petechiae and purpura have developed on the chin, and also violaceous papules and nodules on the face, disappearing without passing through stages of green and yellow discoloration. There are moderately enlarged axillary, right epitrochlear, and left inguinal nodes.

On Aug. 1, 1950, erythematous plaques developed on the chin, cheek, neck, and left anterior axillary fold. The patient received penicillin for two days with no apparent effect. The lesions gradually became purplish, erythematous macules and papules also developed on the palms and soles, with pruritus. There was no antecedent history of drug ingestion, sore throat, or personal or familial allergic tendencies. In the next few weeks intermittent polyarthralgia developed, but with no objective joint changes. On Sept. 17, 1951, the patient manifested acute loss of vision in the left eye, diagnosed as retinal vein thrombosis. Anticoagulant (bishydroxycoumarin [dicumarol®]) therapy was successful in causing all evidence of the central vein thrombosis to disappear, and visual acuity of 20/20 was regained in one month. Skin lesions all disappeared during this period.

In the past four months the patient has continued to have transitory episodes of polyarthralgia. Six weeks ago he again began to manifest erythematous, papular lesions on the palms, accompanied by pruritus and "tightness of the skin." Three weeks ago petechial and purplish lesions began to develop on the hands, feet, face, and left knee.

There has been no fever at any time during the periods of hospitalization (Sept. 20, 1950, to Oct. 25, 1950, and Feb. 6, 1951, to date). The patient is a professional baseball player and was working in July, 1950, prior to the onset of this condition. He has lost 16 lb. (7.3 kg.) since then.

† Dr. Hopkins died on Feb. 27, 1951.

Findings from repeated laboratory studies have shown some variation, but are approximately equivalent to the following report of Feb. 19, 1951: red blood cells, 3,910,000; hemoglobin, 12.2 gm. per 100 cc.; white blood cells, 9,800, with 73% polymorphonuclear leucocytes, 11% lymphocytes, 14% eosinophiles, and 2% monocytes. The coagulation time was five and one-half minutes and bleeding time one minute. Clot retraction was complete in six hours. The prothrombin time was 16.6 seconds, with control 16.7 seconds. The total serum protein was 8.0 gm. per 100 cc. (albumin, 4.8; globulin, 3.2). Results of urinalysis were normal, and the stool contained no ova or parasites. The antistreptococcin titer was 100 to 150 units per cubic centimeter. Blood culture was negative, and culture from a skin lesion also negative. The blood platelets were 299,000, and the erythrocyte sedimentation rate was 45 mm. per hour. Roentgenograms of the joints and chest were normal.

Lymph-node biopsy showed hyperplasia with moderate eosinophilia, not considered diagnostic. Biopsy of the bone marrow showed conspicuous mature eosinophiles but no leukemia. Skin biopsy in October, 1951, showed an eosinophilic infiltrate but no evidence of periarteritis nodosa. Another biopsy in February, 1951, showed thromboarteritis and thromboarteriolitis with eosinophilic reaction. Periarteritis nodosa could not be excluded.

The patient is now receiving bishydroxycoumarin (dicumarol®).

DISCUSSION

DR. GEORGE M. LEWIS: It is an extraordinarily interesting case. Purpuric lesions and the arciform arrangement are sometimes seen in leukemia and in other blood dyscrasias, and I would be interested in the future hematologic findings. The eosinophilia might indicate a beginning eosinophilic leukemia. The suggested diagnosis of periarteritis nodosa is probably the most tenable, although the absence of pain is somewhat against that. The lesions are very superficial, more so than is usual for periarteritis nodosa.

DR. GEORGE C. ANDREWS: I agree that he is a very sick man, and in view of the histologic findings I believe that the tentative diagnosis of periarteritis nodosa should be made. I know of no treatment that can be offered, except that bishydroxycoumarin apparently helped him. Such patients have often had sulfonamides. It is pretty hard for a man of his age to remember these things; somebody may have treated him a few years ago, and he has forgotten about it.

DR. MAURICE J. COSTELLO: The two patients we have had who were treated with cortisone for periarteritis nodosa responded well to small doses.

DR. CARL T. NELSON (by invitation): I agree with Dr. Lewis that one might think of a possible blood dyscrasia in this case. However, it would be difficult to explain the hemorrhagic diathesis on a leukemic basis, since the platelet count is not reduced but is, in fact, elevated. I think he has a vasculitis of some sort, but I do not know whether it is polyarteritis.

DR. HARRY VAN VELSOR (by invitation): I was wondering whether he could not have a type of purpura rheumatica. He has joint symptoms and peculiar subcutaneous swellings, and the blood picture would also fit that diagnosis. The lesions, although they are not minute purpuric spots, are certainly in the purpuric class, and though it is a long history for purpura rheumatica, I think that ought to enter into the differential diagnosis.

DR. FRANK E. CORMIA: I agree with Dr. Andrew. I think it is probably periarteritis nodosa. The eruption certainly is of multiform character, with purpuric lesions and some papules. Erythema multiforme is the commonest cutaneous manifestation of the disease, and from what is stated of the biopsy, the findings are fairly typical. The prognosis has to be guarded. As we all know, and as Rich pointed out many years ago, the severity of the disease varies greatly from patient to patient and may be very mild or may have a fatal outcome.

DR. J. GARDNER HOPKINS: We were very interested in this man. The things that seem to characterize this condition in most cases have been transient swellings, which look like serous inflammatory nodules that just disappear, and persistent eosinophilia, both of which this patient shows. I did not know that arciform lesions of this sort were part of the picture of periarteritis nodosa. To me, the histologic diagnosis has been as difficult as the clinical one. I think there has been a tendency to call it polyarteritis instead of periarteritis, because in many cases we do not find periarteritis. Perhaps I did not emphasize two features of this disease which tend to be confirmatory: (1) the arthralgias, which are unlike those of purpura rheumatica in which the joints are usually red and hot, and (2) the weight loss.

Nevus Pigmentosus (Hairy), Bathing Trunk Distribution. Presented by DR. J. LOWRY MILLER.

DISCUSSION

DR. J. GARDNER HOPKINS: I should like an expression of opinion as to the danger of undertaking therapy in nevus cases.

DR. GEORGE M. LEWIS: There comes a time when you cannot go any further. It is obvious from what Dr. Miller said that it is impossible to excise all the bathing-trunk area, and it would be not only difficult but poor judgment to attempt it. The same does not apply to the prominent pigmented lesions on the scalp and face. Those should be removed, and any others that are conspicuous, so that the boy will not be self-conscious about his appearance.

DR. J. GARDNER HOPKINS: Would you consider the new pigmented macules as possible metastases?

DR. GEORGE M. LEWIS: No, I think rests were there at birth and have developed at this time.

DR. J. GARDNER HOPKINS: What do you think the prognosis is as to life?

DR. GEORGE M. LEWIS: It may be hazardous, but I think the prognosis is good. A man of 55 observed not long ago had had no trouble. From my limited experience I would be optimistic.

DR. GEORGE C. ANDREWS: I feel as Dr. Lewis does that the outlook is optimistic if the lesion is left alone. The small ones can be excised, but I have known children to die after surgeons had attempted to remove such large areas of skin. I have known only one instance of melanoma in this type of bathing trunk nevus, in a man 45 years old. Such patients ordinarily live and get along all right.

DR. JOHN C. GRAHAM: I agree perfectly with the previous speakers. I see no reason to do anything other than to make as good a cosmetic appearance as possible by excising one or two lesions on the face, but I certainly do not feel that further therapy or surgery on the body is indicated in any circumstances.

DR. L. P. BARKER: In areas where the nevus has been excised the pigment is returning darker than before. I think this is often the case when a dark, pigmented nevus of this type is not completely removed. Because of the tremendous size of this lesion, I think it is extremely unwise to give any further treatment.

DR. MAURICE J. COSTELLO: I agree substantially with what Dr. Lewis said, and, as Dr. Barker has mentioned, where the dermatome has been used there is more conspicuous pigment. I do not think the body should ever have been treated. The conspicuous lesions on the face can be removed.

DR. EMMETT S. LUPTON (by invitation): In view of the fact that these new lesions are developing in crops, I would be inclined to put off all treatment until adolescence. I certainly would not touch any lesions on the body. My neighbor's child has extensive lesions; a plastic surgeon operated four times, and three times the skin flaps were pulled together so tensely that they broke open and had to heal by granulation. Once pinch grafts had to be used. The child is terribly scarred and still has a great deal of nevus left. They finally had to use the dermatome too to get skin to put over the areas for cosmetic reasons.

DR. FRANK E. CORMIA: I agree with those who feel that some lesions should be removed, possibly from the face, which is most important cosmetically. I think, however, that any operation should be performed within the next few years, because if cancer supervenes it is more apt to be after puberty. We might learn more about this point by special staining of biopsy sections, in an effort to identify junction-type nevus cells. They might be found on some of the more recently developing lesions.

DR. L. P. BARKER: I would not excise these lesions. I think the cosmetic result is worse than if they are left alone. If any treatment is given, it should be either electrolysis or superficial desiccation; either one would be perfectly safe for this type of nevus.

DR. GEORGE M. LEWIS: This child has dozens of lesions. I imagine he would be cooperative if a few are removed, but I wonder how much difficulty one would experience in treating all lesions with solid carbon dioxide, electrolysis, or any distinctive type of treatment? The logical thing would be to take off the lesions that are conspicuous, by excision probably for the best cosmetic result. If the lesions on the scalp are destroyed by desiccation, a bald spot will result; excision with a thin linear scar would be best. For the lesions on the face, either method would

suffice. We should approach the problem with the attitude that we have all these modalities at our command, and that we can choose the one best suited for the individual lesion.

DR. EMMETT S. LUPTON (by invitation): Did all these small pigmented lesions develop after the plastic surgery?

DR. J. LOWRY MILLER: Yes, within the last two years. I advised removal of the conspicuous lesions on the face. The child is above average mentally, and the parents are both particularly intelligent persons; so they plan to rear him as much as possible as a perfectly normal child, using trunks to cover up the main lesion.

A Case for Diagnosis: Benign Melanosis. Presented by DR. FRANK E. CORMIA.

K. H., a woman aged 42, has good general health. She had a toxic goiter from the age of 17 to 24, with thyroidectomy at 24. She has had urinary frequency for 15 years, corrected on two occasions by removal of a urethral cyst, but bothering her again for the past three years. A year and one-half to two years ago she had an unexplained fever with temperature up to 102 F., of which the cause was undetermined despite extensive investigation.

The present trouble began three years ago with discrete, brown macules on the extensor surfaces of the forearms. One year ago lesions appeared on the thighs, legs, chest, upper part of the back, backs of the hands, and along the sides of the neck. New lesions have continued to appear. The patient has had minimal exposure to sunlight during the past five years.

Slightly scaly, slightly hyperkeratotic, medium-brown macules, 1 to 4 mm. in diameter, are scattered in the locations mentioned. Some lesions are slightly depressed, but there is no obvious atrophy. A few hypopigmentary areas can be noted; the patient states that these were the sites of previous hyperpigmentary lesions. The results of a general physical examination were normal with the exception of slightly irregular pupils which react a little sluggishly to light. No pelvic masses were felt.

Biopsy was performed by a general pathologist, and the main pathologic feature was a considerable deposit of melanin in the basal cells. Hematoxylin-and-eosin- and Masson-stained slides are available for examination. A Mazzini test for syphilis and a blood cholesterol test are being done.

DISCUSSION

DR. GEORGE C. ANDREWS: Lentigo, according to definition, is a brown macule in which there are nevus cells. It is a type of nevus, and entirely different from freckles, or ephelides. Some of our terminology is confusing because one uses one term and one another. I think this patient has freckles, probably, unless biopsy proves that there are nevus cells there, or that they are keratoses. Some of these are nevoid or could come with endocrine changes. She is at the menopause age when she may be getting photosensitization, causing ephelides. I would consider treating her with hormones, vitamin A, and other remedies which influence the pigment of the skin. Adrenal changes also have to be considered.

DR. MAURICE J. COSTELLO: I agree with Dr. Andrews that most of these lesions are prominent on exposed parts of the body and exposed portions of the legs. They are keratoses, especially on the left arm, that have been picked or otherwise injured. The only treatment is to have her avoid exposure to direct sunlight.

DR. EMMETT S. LUPTON (by invitation): I agree with Dr. Andrews. I think that the pigmentation is from some internal disorder and that a determination of the basal metabolic rate would be indicated before ovarian therapy was given.

DR. J. LOWRY MILLER: I agree that the lesions on the arms are of that character. The lesions on the legs did have an additional red pigmentation which could be squeezed out; there is a little angiomatous-type reaction there which tied that up with what we know as spider nevi in liver disorders, and I think that might be the source of the disease. I would be tempted to study the liver function.

Erythema Multiforme of the Oral Mucous Membranes Improved with Cortisone Therapy. Presented by DR. MAURICE J. COSTELLO.

Pemphigus, Responding to (ACTH) But Not to Cortisone. Presented by DR. L. P. BARKER.

Keratosis Follicularis. Presented by DR. FRANK E. CORMIA.

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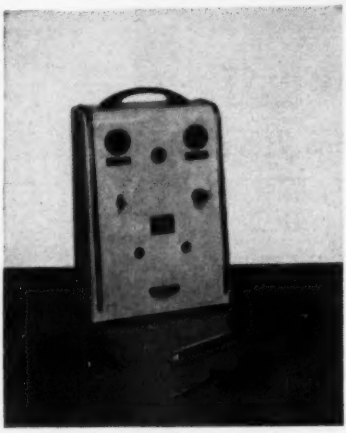

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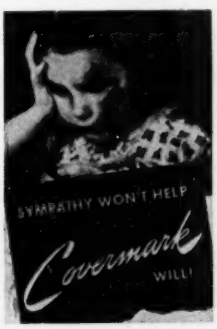

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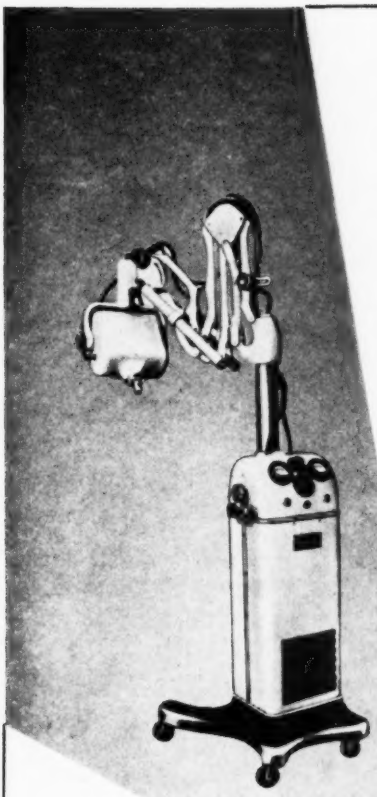

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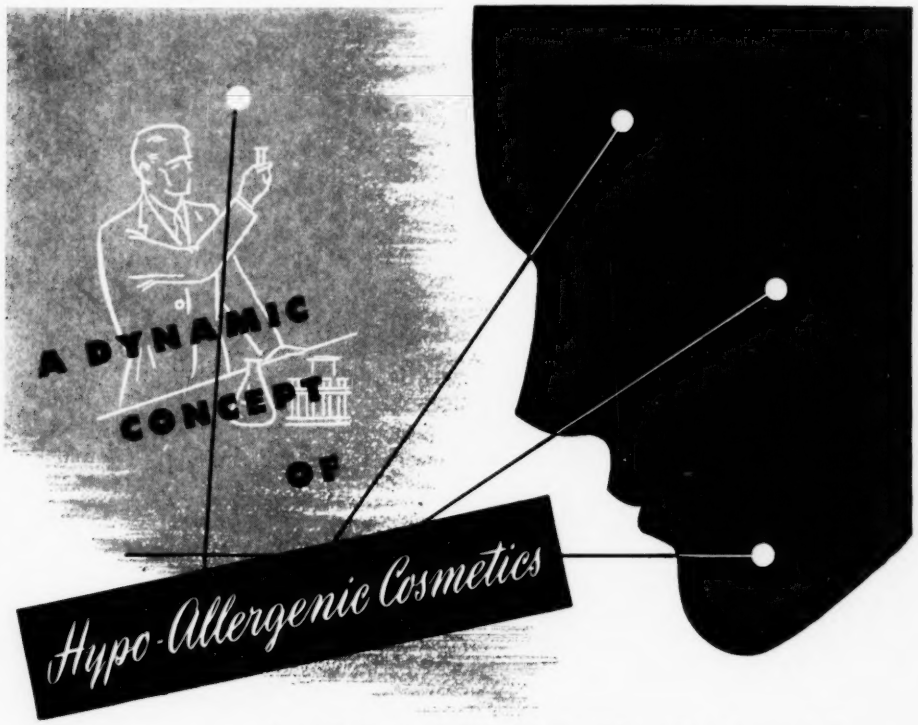

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